KU Leuven
Groep Biomedische Wetenschappen
Faculteit Geneeskunde
Departement Cellulaire en Moleculaire Geneeskunde

Paediatric **E**arly versus Late **Pa**renteral **N**utrition **i**n **C**riticall Illness Multicentre randomised controlled study (**PEPaNIC**)

Tom FIVEZ

Promotor: Prof. Dr. D. Mesotten
Co-Promotor: Prof. Dr. G. Van den Berghe

Proefschrift voorgedragen tot het behalen van de graad van Doctor in de Geneeskunde

Dank u wel…

Dit doctoraatsproject was niet gelukt zonder de hulp van vele mensen.
Vooreerst een oprechte dank aan al de deelnemende kinderen en hun ouders die belangeloos hebben meegewerkt. Dankzij hun medewerking zijn we weer een stap verder gekomen in het optimaliseren van de zorg voor kritiek zieke kinderen.

Ik wens mijn promotor Dieter Mesotten van harte te bedanken. Beste Dieter, het is een intensief en bewogen doctoraat geweest. Doch kan ik me geen betere promotor bedenken. Ik heb bij u mogen groeien als onderzoeker en als persoon. Ik bewonder je respect voor de eigenheid van elk individu en je niet aflatend optimisme. Projectmatig heb je me geleerd om steeds te vertrekken vanuit de basis, het tempo aan te nemen van de traagst lopende opdat enkel zo een project kan slagen. Ik kijk er dan ook naar uit om nog verder met jou projecten uit te bouwen.

Daarnaast wens ik mijn copromotor Greet Van den Berghe te bedanken. Beste Greet, je gaf me de opportuniteit om kliniek en wetenschap te combineren en zo te kunnen deelnemen aan een internationaal project. Zonder je grenzeloze ambitie en passie voor wetenschap gedurende al die jaren, had dit niet mogelijk geweest. Oprecht dank daarvoor.

Pieter, immer paraat als database verantwoordelijke. Zonder uw toewijding zouden de studies niet zijn wat ze zijn. Deze internationale multicentrische studie was ook voor u een bijzondere uitdaging. Heel veel dank voor al het werk.

Sandra en Sylvia, een studie bolt niet zonder onderzoeksverpleegkundigen. Door jullie inzet was het studiegebeuren veelal ontspannend. Dank voor de vele fijne bababels, de leuke en vlotte samenwerking.

Dank aan de staf intensieve geneeskunde en in het bijzonder aan Lars en Dirk. Jullie hebben me met veel passie ingewijd in de kinderintensieve zorgen. Ik heb bijzonder veel geleerd van jullie oprechte toewijding en hoogstaande klinische zorg. Daarnaast dank voor de vele vormende gesprekken.

Dank aan alle verpleegkundigen. Jullie dagelijkse inzet vormt de ruggengraat van de klinische zorg. Ik heb bijzonder graag met jullie samengewerkt. Jullie hebben geen evidente job, maar zorgen ervoor dat de menselijke warme touch behouden blijft in een technische en complexe omgeving.

Dank aan het team in Rotterdam, Koen Joosten, Sascha Verbruggen en Dorian Kerklaan.
Dorian, zonder jouw dagelijkse inzet was er geen PEPaNIC geweest. Dank voor de aangename en vlotte samenwerking gedurende al die jaren.

Dan aan het team in Canada, Ari Joffe, Gonzalo Guerra Garcia en Jan Hanot.
Jan, dank voor het vertrouwen en de durf om mee in dit project te stappen. Je hebt in een nieuwe omgeving de studie getrokken met alle groeipijnen vandien doch bleef je steeds opgewekt en toegewijd.

Dank aan Jenny Gielens voor alle hulp bij het maken van figuren en tabellen en de vele kunstjes in Word, waar ik menigmaal van onder de indruk was.

Dank aan de vrienden en familie rondom mij, rondom ons. Vele van jullie hebben de nodige ups en downs van het project meegevolgd. Bedankt voor de talrijke etentjes, weekends en de open gesprekken. In het bijzonder dank aan Bruno en Katelijne voor de nooit aflatende ondersteuning en joie de vivre.

Bovenal wil ik mijn ouders bedanken. Aan jullie draag ik dit doctoraat op. We hebben mogen opgroeien in alle geborgenheid doch waren jullie er steeds om elke stap aan te moedigen en dit telkens opnieuw. Woorden schieten te kort om jullie te bedanken.

Lieve Eline, zonder jou was dit doctoraat er niet. Jouw eeuwige optimisme en vrolijkheid creëren een heerlijke thuis. Ik verwonder me nog steeds over het gemak waarmee je alles gecombineerd krijgt. Het is een heerlijkheid om met jou door het leven te gaan. Dank voor alles en zoveel meer.

Anna en Marie, mijn twee lieve deugenieten. Het is schitterend om jullie erbij te hebben. Steeds zorgen jullie voor de nodige afleiding en relativering. Ik kijk ernaar uit om jullie te zien opgroeien.

Tom

Table of Content

List of abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
BG	Blood Glucose
CHO	Carbohydrate
CT	Computer Tomography
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EE	Energy Expenditure
EN	Enteral Nutrition
EPANIC	Impact of withholding early parenteral nutrition completing enteral nutrition in critically ill patients
ESPEN	European Society for Clinical Nutrition and Metabolism
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
ESPNIC	European Society of Paediatric and Neonatal Intensive Care
ICC	Intraclass Correlation Coefficient
ICU	Intensive Care Unit
ICU-AW	Intensive Care Unit-Acquired Weakness
IQR	Inter Quartile Range
LOS	Length Of Stay
MRC	Medical research council
MRI	Magnetic Resonance Imaging
PDMS	Patient Data Management System
PELOD	Pediatric Logistic Organ Dysfunction
PEPANIC	Impact of Withholding Early Parenteral Nutrition Completing Enteral Nutrition in Pediatric Critically Ill Patients
PICU	Pediatric Intensive Care Unit
PN	Parenteral Nutrition
PRISM	Pediatric RISK of Mortality

RACHS	Risk-Adjustment in Congenital Heart Surgery
RCT	Randomized Controlled Trial
RDA	Recommended Dietary Allowances
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SD	Standard Deviation
US	Ultrasonography
WFPICCS	World Federation of Pediatric Intensive and Critical Care Societies

1. General Introduction

A brief history of pediatric critical care medicine

Pediatric critical care is a new discipline in medicine, emerging only 60 years ago.(1)

Five crucial developments in the 1950's were essential for the development of pediatric critical care medicine, namely the polio epidemic, the respiratory distress syndrome and breakthroughs in pediatric anesthesiology, surgery and cardiac surgery. The polio epidemic led to the development of the mechanical ventilators. It was Dr. Ibsen in Copenhagen who took the initiative to ventilate patients manually after they underwent a tracheotomy and received rubber cuff tubes.(2) He organized a special unit for respiratory care where he employed nurses, medical students and technicians to work around the clock. Thanks to their efforts polio-related mortality decreased from 90% to 40%. These special units also cared for children, but they quickly understood that children needed separate units. In 1955 Dr. G Haglund in Goteburg, Sweden founded the first pediatric ICU.(3)

The understanding of the infant respiratory distress syndrome and its treatment with surfactant led in 1960 to the survival of children with chronic lung disease, termed bronchopulmonary dysplasia. These children needed pediatric intensive care after their discharge from neonatology.

Dr. E Koop, was a brilliant and courageous pediatric surgeon who pioneered many surgical techniques in the 1950's and was the first to create a special postsurgical care unit for children in Children's Hospital of Philadelphia (CHOP). Together with Dr. W Rashkind (father of the interventional pediatric cardiology), Dr. J Waldhausen (one of the first full time pediatric cardiac surgeons), Dr. Sylvan Stool (a pioneer in pediatric otolaryngology) they further developed this unit.

The first extra cardiac shunt between the subclavian artery and the ipsilateral pulmonary artery was performed the first in the John Hopkins hospital in 1945 by Alfred Blalock, Vivien Thomas and Helen

Taussig. The first open-heart surgery on a child with cardiopulmonary bypass was done by J. Gibbon in 1953. Thanks to the anesthesiologists who transferred their knowledge of pediatric physiology and pharmacology these postoperative pediatric critical care units were established and grew over the years.

The recognition of the subspecialty of pediatric critical care took place in 1981. In 1983 guidelines defining the minimal requirements of a PICU became available. Nowadays pediatric critical care medicine is an exciting combination of high standard multidisciplinary medicine involving many medical specialties and the unique aspect of the patient's childhood. The pediatric intensivist has to preserve a plan for each of the patients in close communication with all stakeholders (parents, specialists, nurses, physiotherapists etc..) involved. This complex task is in many ways rewarding but also demanding.

Due to the technological and medical advances in the following decades, mortality in the PICU has significantly declined. But therefore nowaday's PICU population has also become more complex. Not only children with more serious diseases are treated or operated on before being admitted to the PICU. Critically ill children are also more often confronted with multiple organ dysfunction and consequently prolonged critical illness. The increase in prevalence of prolonged critical illness, hallmarked by intensive care- unit acquired weakness (ICUAW), faces the pediatric intensivist with new ethical problems.

Similar to the shift in adult ICU population, the focus of clinical practice and research should be based on a combination of hard clinical outcome measures in the long-term such as 90 mortality, new infections and ventilator dependency and of quality of life up to several years after hospital discharge.

Despite that this is time consuming and most labor-intensive, knowing if and how the critically ill patients survive is crucial for all stakeholders from patients to health policy makers.

Muscle Wasting

Prolonged critical illness is frequently hallmarked by intensive care unit-acquired weakness (ICUAW). ICUAW is typically symmetrical and more pronounced in the proximal muscles than in the distal muscles.(4, 5) It is related to the severity of illness and the length of stay in ICU. However, ICUAW already starts within the first week of critical illness and is associated with functional disability in the longer term. The ICUAW is the result of critical illness polyneuropathy (CIP) or critical illness myopathy (CIM) or a combination of both. Skeletal muscle wasting is the most typical clinical feature of ICUAW and is due to muscle fiber degradation and decreased synthesis. A detailed overview of the molecular mechanisms behind ICUAW has recently been published.(6-8) The main risk factors for ICUAW are high severity of illness upon admission, sepsis, multiple organ failure, prolonged immobilization, hyperglycemia and older age.(5)

ICUAW is associated with prolonged mechanical ventilation, longer ICU and hospital stay and increased mortality. In the longer-term, it also impairs rehabilitation and recovery, leading to poor quality of life.(9, 10) A systematic review indicated that 28% of patents suffered from severe sequellae of ICUAW.(11) Unfortunately therapeutic interventions are limited to early mobilization, blood glucose control, aggressive treatment of sepsis and limiting the use of glucocorticoids and neuromuscular blocking agents.(11, 12)

ICUAW is poorly described in children.(13) It is more difficult to diagnose, as strength measurements are only possible and validated from the age of 6 onwards. These muscle strength measurements, such as the Medical Research Council (MRC)-SUM test, are the gold standard for diagnosing ICUAW.(14) However, these tests require cooperative patients and thus cannot be applied in sedated children or infants.

Quantification of muscle wasting

Due to the lack of therapeutic options and the important long-term consequences of ICUAW and muscle wasting, their early detection may be essential to steer risk stratification and preventative measures. Assessment of limb muscle strength by functional, volitional measurements, such as the Medical Research Council (MRC)-sum score and handgrip strength, is the gold standard.(15) However, only fully awake and cooperative patients can undergo these measurements, potentially causing a delay in the diagnosis of ICUAW.(10) Therefore, non-volitional muscle strength measurements, such as an electromyogram to detect critical illness polyneuropathy and myopathy, have been used for the early screening for ICUAW. Unfortunately, this technique is complex, requiring expert's interpretation.(12)

Ultrasound measurements of muscle thickness are also considered to be a non-volitional surrogate for muscle strength.(16) The use of ultrasonography is well integrated in daily ICU-practice. In comparison with computer tomography (CT) and magnetic resonance imaging (MRI), ultrasound measurements of muscle thickness are inexpensive and logistically less cumbersome. When using a strict imaging protocol, the ultrasound measurements correlate well with the CT and MRI measurements.(10, 16, 17) In adult critically ill patients ultrasound measurements of m. quadriceps femoris muscle thickness were sensitive to detect a decrease in muscle mass in patients with a prolonged ICU-stay.(6) In a recent prospective, ultrasonographical evaluation of muscle wasting in critically ill patients, rectus femoris cross-sectional area was decreased by approximately 18% at day 10.(18) The recent paper of Tilluist et al. highlighted the reliability of bedside ultrasound in assessing muscle thickness in healthy volunteers.(19)

However ICUAW is poorly characterized in children, with only case reports as evidence(13, 20). Neither the functional, volitional measurements of muscle strength nor the non-volitional measurements of muscle mass, such as ultrasonography have been validated in the pediatric critically ill patient population.

Additionally, ultrasonographical measurements of muscle mass are harder to standardize due to the age-dependency of muscle mass.

Energy requirements

Metabolic Response To Acute Injury

The common thought has always been that a decreased energy provision to skeletal muscle plays a key role in skeletal muscle wasting and ICUAW. Due to acute critical illness, the patient cannot eat normally and is thus confronted with caloric deficit, which will build up during ICU-stay. The caloric deficit is a function of the patient's energy requirements and the amount of calories delivered to the patient.

Resting Energy Expenditure

Total energy expenditure is the energy generated by oxidative metabolism and is subdivided in four components. The most important component is the basal metabolic rate (BMR) (70% of EE). This is the energy needed to sustain all vital processes. The second component is the energy needed for growth (5-35% of EE, depending on the age of the child). Diet-induced thermogenesis (4-10% of EE) is the third component. Physical activity, the forth component, is variable and typically expressed as multiples of BMR.

Determining the caloric needs of infants and children on the PICU starts with the estimation of the resting energy expenditure, as physical activity is minimal. The REE is defined as the amount of calories needed at rest during a 24 hour period. It is closely related to the BMR but not exactly the same. The REE can be determined either by standard equations or by the use of indirect calorimetry.(21-25) There are many equations available to predict the EE in children (Table 1). Their accuracy in critical ill children is however not clear. For example the Harris Benedict equation is often used in PICU for children, however the formula itself is based on measurements made on 97 infants < 8 days of age and on 239 individuals > 16 years of age.(21) The Harris Benedict equation has thus never been validated for children.

Despite the common use of these formulas, concordance with energy expenditure has not been shown.

REE can be measured indirectly with a metabolic cart, using the analysis of expired gases to derive the volume of air that passes through the lungs, the amount of oxygen extracted from it (VO2) and the amount of carbon dioxide that is produced (VCO2).(26) The latter immediately reveals a major conceptual problem, namely that with the use of this technique we can only measure what is produced as CO2. The technique is also time consuming. Moreover, when the inspired fraction of oxygen is above 40%, the measurements are not reliable, making indirect calorimetry unusable in the sickest children, who often need the highest fraction of oxygen. There is also a high variability of results with the different types of indirect calorimeters.(27) The many equations available and the limited use of indirect calorimetry lead to wide variations in caloric goals used in the PICU worldwide.

Many nutritional experts advocate that correction factors should be used to account for the severity of illness, because these experts assume that children who are critically ill need even more nutrition. Nevertheless, the latter is not standardized nor supported by high quality research.

Table 1

Harris-Benedict equation (kcal/d)

Boys: 66.4730 + (5.0033 * height) + (13.7516 * weight) - (6.7550 * age)

Girls: 655.0955 + (1.8496 * height) + (9.5634 * weight) - (4.6756 * age)

Schofield equations (kj/d) (1 kcal ¼ 4.186 kj)

< 3 y	Boys:	(0.0007 * weight) + (6.349 * height) - 2.584
	Girls:	(0.068 *weight) + (4.281 * height) - 1.730
3–10 y	Boys:	(0.082 * weight) + (0.545 * height) + 1.736
	Girls:	(0.071 * weight) + (0.677 * height) + 1.553
10–18 y	Boys:	(0.068 * weight) + (0.574 * height) + 2.157
	Girls:	(0.035 * weight) + (1.948 * height) + 0.837

FAO/WHO/UNU equations

< 3 y	Boys:	(kcal/d): (60.9 * weight) - 54
	Girls:	(kcal/d): (61 * weight) - 51
3–10 y old (1 kcal ¼ 4.186 kJ)		
	Boys:	(kJ/g): (95 * weight) + 2071
	Girls:	(kJ/d): (94 * weight) + 2088
10–18 y	Boys:	(kcal/d): (16.6 * weight) + (77 * height) + 572
	Girls	(kcal/d): (7.4 * weight) + (482 * height) + 217

Maffeis equations (kJ/d) (1 kcal ¼ 4.186 kJ)

Boys: (28.6 * weight) + (23.6 * height) - (69.1 * age) + 1287

Girls: (35.8 * weight) + (15.6 * height) - (36.3 * age) + 1552

Fleisch equation (kcal/d)

Boys: 1–12 y: 24 * BSA * (54-0.885 * age)

13–19 y: 24 * BSA * (42.5 - [0.64 * (28)])

Girls: 1–10 y: 24 * BSA * (54-1.045 * age)

11–19 y: 24 * BSA * (42.5 - [0.778 * (28)])

BSA, body surface area; FAO/WHO/UNU, Food and Agriculture Organization/ World Health Organization/United Nations University;

Artificial Nutrition

Critical illness results in anorexia, a caloric deficit, muscle wasting and a profound catabolic response. Critical illness is also supposed to give higher energy needs, certainly in the second “flow” phase. In order to meet these energy needs and to prevent protein loss , nutrition is initiated by the physician. As most of the patients admitted to the PICU are incapable of eating, artificial nutrition is commonly used.

Artificial nutrition is the combination of macronutrients (lipids, carbohydrates and proteins) and micronutrients (vitamins and trace elements). The artificial nutrition can be given directly into the vein (parenteral nutrition), or in the gastrointestinal tract (enteral nutrition).

Enteral nutrition

The enteral route is preferred as it has been suggested that feeding via the gut maintains gut integrity and may reduce the risk of infection, in comparison with feeding via the parenteral route. The composition of enteral nutrition for neonates is based on breast milk. For older children the protein and energy load of enteral nutrition is higher.

The delivery of enteral nutrition in PICU population is challenging, due to intolerance to enteral nutrition. Not only commonly administered medications, such as opioids, but also critical illness itself impairs the gastric intestinal motility. On top of that the physicians’ treatments, such as fluid restriction and extubation, result in frequent interruptions of administration of enteral feeding.

The timing of EN for critically ill children has mostly been studied in children with burns. An RCT of early (within 24 hours) versus conventional (after 48 hours) initiation of EN in 77 children with burns showed no effect on either surrogate outcome measures (nitrogen balance, serum (pre)albumin), nor on hard clinical outcomes (mortality, sepsis, length of stay) (29). However, in a more recent RCT by Khorasani et al in 688

children with burns, early EN (started within 3-6 hours) was associated with a lower mortality rate, shorter hospital stay and less weight loss compared to children receiving late EN (after 48 hours) (30).

Other RCTs on EN in critically ill infants and children mainly focused on the amount of protein. In a number of studies in infants and children receiving high protein EN compared to normal diet, protein synthesis and plasma levels of essential and branched chain amino acids were increased (31-34). Only one RCT was powered to detect clinical outcome parameters and found that survival improved with high protein enteral intake in children with burns (35). Children receiving normal protein enteral nutrition also had more bacteriemic days and days on antibiotics.

Parenteral Nutrition

The first experiments with parenteral nutrition on dogs date from 1966 (36). Before that time it was difficult to achieve intravenous access as sharp metal needles were used and stayed in place. Moreover as the IV solutions were given peripherally, they had to be iso-osmotic. This was a second hindrance as this required large amounts of fluid in a time when effective IV diuretics were not available. A pioneer study in dogs showed however that they could be successfully fed solely parenterally. In 1968 a child got for the first time parenteral nutrition. A neonate with small bowel atresia, who was moribund after extensive bowel resection and weighted only 1.8 kg, was effectively fed parenterally for 22 months and achieved a maximum weight of 8.3 kg. Clinicians gained during her treatment essential technical and metabolic insights(37).

Since the 1970's parenteral nutrition has been used more routinely in adult and pediatric ICUs. Guidelines on how to administer parenteral nutrition during pediatric critical illness have evolved over the following decades. As more parenteral nutrition solutions became commercially available, focus was very much on the composition of parenteral nutrition (mixture of amino acids, type of lipids). Similar to timing of EN, the classically held dogma has been that caloric deficits should be minimized. Parenteral nutrition should be used when EN alone cannot meet the child's caloric needs. The current guidelines on energy requirements

in critically ill children and the prevention of caloric deficits are not detailed. The ESPEN (European Society for Clinical Nutrition and Metabolism)/ESPGHAN (European Society for Paediatric Gastroenterology Hepatology and Nutrition) guidelines state that the initiation of PN depends on the individual circumstances and the age and size of the infant or child (3). They advocate starting PN shortly after admission when EN fails, but in older children and adolescents longer periods of inadequate nutrition can be tolerated. In brief, current age-related recommendations advise glucose infusion for hospitalized children in the range of 2-13 mg/kg/min and to limit it to around 5 mg/kg/min in critically ill children(6). Protein intake during critical illness may be up to 2-3 g/kg/day, dependent on the age, to improve the nitrogen balance (6). The requirements of specific amino acid concentrations are still unclear. Free fatty acids remain the primary source of energy under inflammatory stress(4). Lipid provision should be 30 % to 40 % of the non-protein calories to a maximum of 3-4 g/kg.day in infants and 2-3 g/kg.day in older children. The American A.S.P.E.N. (American Society for Parenteral and Enteral Nutrition) guidelines make no recommendations concerning PN on the PICU(1). They only state that in older children a caloric deficit can be tolerated for up to a week.

These recommendations have been mainly based on expert opinion and not on state-of-the-art randomized controlled trials. Surprisingly, never the real question whether parenteral nutrition per se is beneficial in critically ill children has been asked.

References

1. Downes JJ. The historical evolution, current status, and prospective development of pediatric critical care. Crit Care Clin. 1992 Jan;8(1):1-22.

2. Ibsen B. [Organization of an intensive care unit in Copenhagen. Retrospective and prospective studies]. Der Anaesthesist. 1968 Aug;17(8):272-7. Organisation einer Intensivtherapieabteilung in Kopenhagen. Ruckblick und Ausblick.

3. Haglund G. Respiratory treatment in polio epidemics 1953-1961. Acta anaesthesiologica Scandinavica Supplementum. 1962;12:25-9.

4. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013 Oct 16;310(15):1591-600.

5. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Clinical review: Critical illness polyneuropathy and myopathy. Crit Care. 2008;12(6):238.

6. Puthucheary Z, Montgomery H, Moxham J, Harridge S, Hart N. Structure to function: muscle failure in critically ill patients. The Journal of physiology. 2010 Dec 1;588(Pt 23):4641-8. PubMed PMID: 20961998.

7. Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. Am J Respir Crit Care Med. 2013 Feb 1;187(3):238-46.

8. Friedrich O, Reid MB, Van den Berghe G, Vanhorebeek I, Hermans G, Rich MM, et al. The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. Physiol Rev. 2015 Jul;95(3):1025-109. PubMed PMID: 26133937.

9. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011 Apr 7;364(14):1293-304.

10. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute outcomes and 1-year mortality of intensive care unit-acquired weakness. A cohort study and propensity-matched analysis. Am J Respir Crit Care Med. 2014 Aug 15;190(4):410-20.

11. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev. 2014;1:CD006832.

12. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014 Apr 24;370(17):1626-35.

13. Williams S, Horrocks IA, Ouvrier RA, Gillis J, Ryan MM. Critical illness polyneuropathy and myopathy in pediatric intensive care: A review. Pediatr Crit Care Med. 2007 Jan;8(1):18-22.

14. Vanpee G, Hermans G, Segers J, Gosselink R. Assessment of limb muscle strength in critically ill patients: a systematic review. Crit Care Med. 2014 Mar;42(3):701-11.

15. Hermans G, Clerckx B, Vanhullebusch T, Segers J, Vanpee G, Robbeets C, et al. Interobserver agreement of Medical Research Council sum-score and handgrip strength in the intensive care unit. Muscle & nerve. 2012 Jan;45(1):18-25.

.

16. Arbeille P, Kerbeci P, Capri A, Dannaud C, Trappe SW, Trappe TA. Quantification of muscle volume by echography: comparison with MRI data on subjects in long-term bed rest. Ultrasound in medicine & biology. 2009 Jul;35(7):1092-7.

17. Dupont AC, Sauerbrei EE, Fenton PV, Shragge PC, Loeb GE, Richmond FJ. Real-time sonography to estimate muscle thickness: comparison with MRI and CT. Journal of clinical ultrasound : JCU. 2001 May;29(4):230-6.

18. Grimm A, Teschner U, Porzelius C, Ludewig K, Zielske J, Witte OW, et al. Muscle ultrasound for early assessment of critical illness neuromyopathy in severe sepsis. Crit Care. 2013;17(5):R227.

19. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. JPEN J Parenter Enteral Nutr. 2014 Sep;38(7):886-90.

20. Kukreti V, Shamim M, Khilnani P. Intensive care unit acquired weakness in children: Critical illness polyneuropathy and myopathy. Indian J Crit Care Med. 2014 Feb;18(2):95-101.

21. Harris JA, Benedict FG. A Biometric Study of Human Basal Metabolism. Proc Natl Acad Sci U S A. 1918 Dec;4(12):370-3.

22. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Human nutrition Clinical nutrition. 1985;39 Suppl 1:5-41

23. Energy and protein requirements: report of a joint FAO-WHO ad hoc expert committee. Rome, 22 March - 2 April 1971. World Health Organization technical report series. 1973;522:1-118.

24. Maffeis C, Schutz Y, Micciolo R, Zoccante L, Pinelli L. Resting metabolic rate in six- to ten-year-old obese and nonobese children. J Pediatr. 1993 Apr;122(4):556-62.

25. Verhoeven JJ, Hazelzet JA, van der Voort E, Joosten KF. Comparison of measured and predicted energy expenditure in mechanically ventilated children. Intensive Care Med. 1998 May;24(5):464-8.

26. Joosten KF. Why indirect calorimetry in critically ill patients: what do we want to measure? Intensive Care Med. 2001 Jul;27(7):1107-9.

27. Sundstrom M, Tjader I, Rooyackers O, Wernerman J. Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr. 2013 Feb;32(1):118-21.

28. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep 12;352(9131):854-65.

29. Gottschlich MM, Jenkins ME, Mayes T, Khoury J, Kagan RJ, Warden GD. The 2002 Clinical Research Award. An evaluation of the safety of early vs delayed enteral support and effects on clinical, nutritional, and endocrine outcomes after severe burns. J Burn Care Rehabil. 2002 Nov-Dec;23(6):401-15.

30. Khorasani EN, Mansouri F. Effect of early enteral nutrition on morbidity and mortality in children with burns. Burns. 2010 Nov;36(7):1067-71.

31. Patterson BW, Nguyen T, Pierre E, Herndon DN, Wolfe RR. Urea and protein metabolism in burned children: effect of dietary protein intake. Metabolism: clinical and experimental. 1997 May;46(5):573-8.

32. van Waardenburg DA, de Betue CT, Goudoever JB, Zimmermann LJ, Joosten KF. Critically ill infants benefit from early administration of protein and energy-enriched formula: a randomized controlled trial. Clin Nutr. 2009 Jun;28(3):249-55.

33. de Betue CT, van Waardenburg DA, Deutz NE, van Eijk HM, van Goudoever JB, Luiking YC, et al. Increased protein-energy intake promotes anabolism in critically ill infants with viral bronchiolitis: a double-blind randomised controlled trial. Arch Dis Child. 2011 Sep;96(9):817-22.

34. Botran M, Lopez-Herce J, Mencia S, Urbano J, Solana MJ, Garcia A. Enteral nutrition in the critically ill child: comparison of standard and protein-enriched diets. J Pediatr. 2011 Jul;159(1):27-32 e1.

35. Alexander JW, MacMillan BG, Stinnett JD, Ogle CK, Bozian RC, Fischer JE, et al. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg. 1980;192(4):505-17.

36. Dudrick SJ, Steiger E, Wilmore DW, Vars HM. Continuous long-term intravenous infusion in unrestrained animals. Lab Anim Care. 1970 Jun;20(3):521-9.

37. Wilmore DW, Dudrick SJ. Growth and development of an infant receiving all nutrients exclusively by vein. JAMA. 1968 Mar 4;203(10):860-4.

2. Aim and Study Objectives

The aim of this PhD project is to gain understanding in the clinical effect and the current practice of supplementing parenteral nutrition when enteral nutrition is insufficient in pediatric patients during critical illness.

In the first part (chapter 3,4) we study the current nutritional practice in pediatric critical ill patients. Firstly we performed a systematic review to identify randomized controlled trials about the timing of supplemental parenteral nutrition. Since the current guidelines for children about nutritional support during critical illness are not detailed, we hypothesized in our survey that these guidelines would result in a very variable practice worldwide.

In the second part (chapter 5) we examined the methodological quality of ultrasonography to diagnose muscle wasting in children during critical illness.

In the third part (chapter 6,7) we planned (chapter 6), conducted and analyzed (chapter 7) an international randomized multicenter clinical trial with the acronym PEPaNIC, comparing *early-PN* to *late-PN*. In the *early-PN* group parenteral nutrition was initiated within two days after ICU admission unless enteral nutrition was sufficient or oral intake was expected to resume. In the *Late-PN* group, no PN was administered before day 8 after ICU admission.

3. Systematic Review: Parenteral nutrition in the Pediatric Intensive Care Unit

Adapted from:

Fivez T, Kerklaan D*, Mesotten D, Verbruggen S, Joosten K, Van den Berghe G. Evidence for the use of parenteral nutrition in the pediatric intensive care unit, Clinical Nutrition (2015)*

** Equal contribution*

Abstract

Background and Aims: During hospitalization in a pediatric intensive care unit (PICU), critically ill children are fed artificially. Administered via the preferred enteral route, caloric targets are often not reached. Hence, parenteral nutrition is given to this patient population. In this review we analyzed the available evidence from randomized controlled trials (RCTs) that supports the use of parenteral nutrition in children during critical illness.

Methods: A search strategy in Ovid MEDLINE and Ovid EMBASE was created and trial registries were screened to identify the relevant RCTs. Studies were included if they were randomized controlled trials, involved pediatric patients admitted to PICU, and compared different dosing/compositions of parenteral nutrition. Descriptive studies and reviews were excluded.

Results: Of the 584 articles identified by the search strategy, only 114 articles were retained after title screening. Further abstract and full text screening identified 6 small RCTs that compared two dosing/composition strategies of parenteral nutrition. These trials reported differences in surrogate endpoints without an effect on hard clinical endpoints. The RCTs observed improvements in these surrogate endpoints with the use of more calories or when parenteral glutamine or fish oil was added.

Conclusions: The few RCTs suggest that surrogate endpoints can be affected by providing parenteral nutrition to critically ill children, but the studies were not statistically powered to draw meaningful clinical conclusions. Large RCTs with clinically relevant outcome measures are urgently needed to support the current nutritional guidelines that advise the use of parenteral nutrition in the PICU.

Introduction

For critically ill children who require an admission to the Pediatric Intensive Care Unit (PICU), nutritional support is advised as soon as possible to prevent or reduce catabolism, with the intention to enhance recovery while allowing normal growth (1). The enteral route is preferred as it has been suggested that feeding via the gut maintains gut integrity and may reduce the risk of infection, in comparison with feeding via the parenteral route (1). However, when only enteral nutrition (EN) is provided during PICU-stay, caloric targets are often not reached. This is explained by intestinal dysfunction as part of the critical illness, the administered medication that affects the gastro-intestinal tract, frequent interruptions of enteral feeding and the need for fluid restriction (2). Hence, a caloric deficit quickly builds up in critically ill children, the severity of which has been associated with poor outcomes and impaired growth (3, 4). Children are particularly vulnerable for accumulating a pronounced caloric deficit as their relative energy requirements are 2-3 times higher than those of adults. Reaching the preset caloric targets is easier when parenteral nutrition (PN) is administered. However, feeding children via the parenteral route has shown to increase the risk of metabolic disturbances such as hyperglycemia and dyslipidemia and to be associated with more nosocomial infections (5). Therefore, the question remains if, and when, PN should be initiated for critically ill children in the PICU.

The currently available guidelines are not very specific on how energy requirements should be determined for critically ill children nor on how the caloric deficit should best be prevented. The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines state that the initiation of PN depends on the clinical condition and the age and size of the infant or child (6). These guidelines advocate to start PN in infants shortly after admission to PICU whenever EN fails, but in older children and adolescents longer periods of inadequate nutrition may be tolerated. The American Society for Parenteral and Enteral Nutrition

(A.S.P.E.N.) guidelines make no specific recommendations for the use and dosing of PN for children treated in the PICU (1). However, the A.S.P.E.N. guidelines state that for older children, a caloric deficit can be tolerated for up to one week. These different and rather non-specific recommendations have resulted in nutritional practices that vary widely among PICUs worldwide (7).

Therefore, we performed an up to date review to assess all available evidence from randomized controlled trials (RCTs), with hard clinical as well as surrogate endpoints, that supports the use of parenteral nutrition in children during critical illness.

Methods

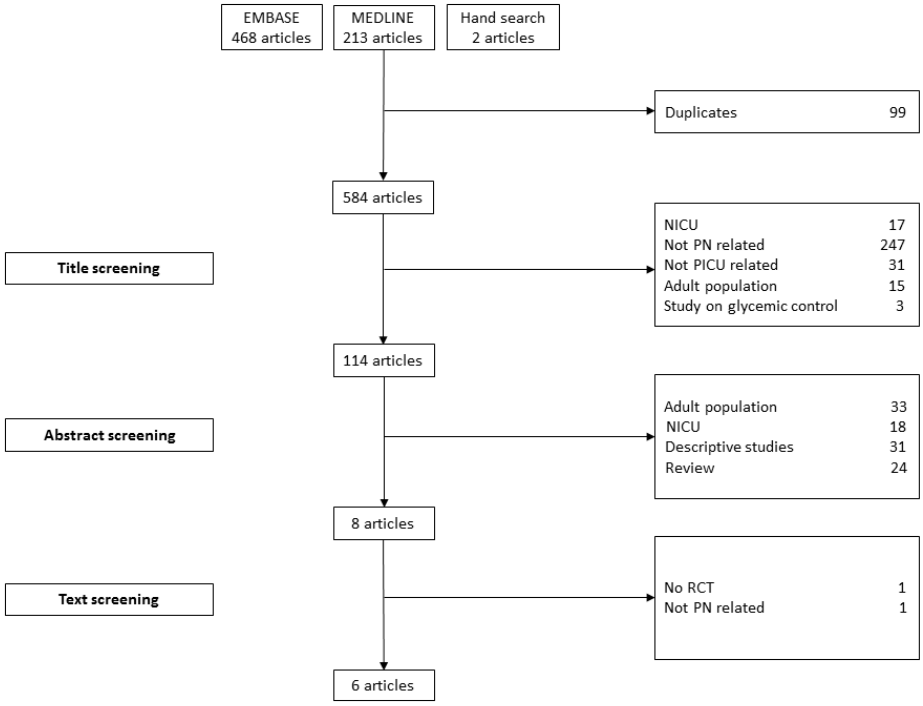
An extensive search strategy in both Ovid MEDLINE and Ovid EMBASE was created and trial registries were screened to identify the relevant RCTs. Studies were included if they were randomized controlled trials, involved pediatric patients admitted to PICU, and compared different dosing/compositions of parenteral nutrition. Parenteral nutrition was defined as intravenously administered macronutrients (carbohydrates, lipids, proteins) of which dosing differed between treatment groups in the included RCT's.

The time frame of the search strategy was from the inception of these databases up to September 7, 2015. Also non-English language studies were taken into account. In addition, trial registries were screened and reference lists of all potentially relevant studies were analyzed manually. The detailed search strategies are described in Appendix 1. We included only randomized controlled trials, and any eventual post-hoc analyses thereof, of pediatric patients admitted to the PICU that compared different dosing/compositions of parenteral nutrition. Descriptive studies and reviews were excluded. Also studies involving the adult or premature newborn population were excluded. We focused on timing and dosing as well as composition of parenteral macronutrients and did not address other nutritional aspects in the PICU. The initial focus was on studies with hard clinical outcome measures (such as infections, length of PICU stay in PICU, or mortality). However, a systematic review from 2009 revealed that one study used a clinical outcome measure. Therefore, we also included studies with surrogate endpoints (such as nitrogen balance or markers of inflammation). The quality assessment of the individual studies was based on the Jadad score (8) and the Black and Downs score (9).

Two authors (TF, DK) independently screened the search results. Two selection criteria were premised for title and abstract screening. First, the study population had to consist of term neonates, infants, children or adolescents treated in the PICU. Secondly, the studies needed to investigate parenteral nutritional support during hospitalization in PICU. For the full text screening, these criteria were further narrowed to (a) an age range of 37 weeks gestational age to 18 years of age and (b) to randomized controlled trials in which dosing

and/or timing of mixed-bag PN or one of its components (amino acids, lipids, glucose) differed between the randomly allocated groups. Hence, studies comparing EN strategies were excluded. TF and DK independently determined eligibility. In case of discrepancy, SV and KJ decided on inclusion by consensus.

Figure 1: Flowchart of screening process



Results

After title screening, 114 articles were retained (Fig 1). The main reasons for these initial exclusions were (a) non-PN related aspects of nutrition, such as dosing of EN and (b) non-randomized controlled trials. After further screening of the abstracts and an additional manual search, 8 articles were retained (10-17). Of these, full text reading resulted in exclusion of another 2 articles, one that was related to EN instead of PN and one was not a RCT (15, 16). Table 1 gives an overview of the 6 trials, of which 1 was a post-hoc analysis of one of 5 RCTs (11), that were identified as relevant for this review. As the retained studies used different interventions and outcome measures they could not be analyzed in a formal meta-analysis.

The RCT by Larsen et al., as well as the post hoc analysis of this RCT, investigated 32 infants undergoing elective open-heart surgery with cardiopulmonary bypass and compared the effect of the pre- and post-operative administration of two types of parenteral lipid formulas, namely Intralipid® (LCT soybean oil) in the control group and Lipoplus® (50% MCT, 40% LCT, 10% Fish oil) in the intervention group (11, 17). In the primary trial (17), the authors report significantly lower plasma concentrations of TNF-alpha and IL-6 (primary outcome measures) on the first postoperative day in the treatment group receiving Lipoplus®. On day 7, the plasma TNF-alpha and IL-6 concentrations were no longer different. Also duration of stay in PICU/hospital, incidence of sepsis, inotrope scores or ventilator days (secondary outcome measures) were similar in both groups. The post hoc analysis (11) also reported lower levels of other inflammation biomarkers (procalcitonin, leukotriene B4, lymphocytes) in the Lipoplus® group.

Two RCTs by Chaloupecky et al. were studies of 29 and 37 infants, respectively, undergoing cardiac surgery, in which the impact on proteolysis and plasma amino-acid profiles of early parenteral administration of a higher dose of amino-acids and of glucose as compared with a low dose maintenance glucose infusion on the first postoperative day was investigated (10, 12). Thereafter, all patients received enteral nutrition in equal amounts. The authors reported less negative nitrogen balances, less proteolysis as suggested by urinary 3-methylhistidine excretion, and higher levels of plasma amino acids during the first

postoperative day in the intervention group who received more parenteral amino acids and glucose. Although clinical outcome measures were not explicitly described, the authors report no severe complications such as low cardiac output syndrome, renal failure, sepsis or mortality in any of the groups. Duration of intubation and inotropic support did not differ between treatment groups.

The RCT by Jordan et al. investigated 98 children suffering from severe sepsis or admitted after major surgery who were identified as requiring parenteral nutrition. The study compared the impact of glutamine-supplemented parenteral nutrition in the intervention group with standard parenteral nutrition in the control arm (13). The authors report that glutamine-supplemented parenteral nutrition evoked a higher plasma concentrations of heat shock protein 70 on day 5, whereas plasma concentrations of IL- 6 and IL-10 were not affected. Clinical outcome measures were not significantly different in the 2 study groups.

The RCT by Lekmanov et al. studied 40 children with severe thermic burns and concomitant injuries and compared the effect of glutamine-supplemented total parenteral nutrition during at least one week in the intervention group to standard total parenteral nutrition in the control group (14). The authors reported no significant differences between the two groups for the serum levels of protein, albumin and glutamine on day 5 and 7 of PICU stay, but found a significantly shorter duration of mechanical ventilation in the intervention group (7 days versus 12 days in the control group). This result should be interpreted with caution, since the methods section was incomplete without information on the statistical analyses. Also plasma concentrations of glutamine were not significantly different between the two groups.

Quality assessment revealed low scores for the 2 RCTs by Chaloupecky et al.; namely a Jadad score of 1 and a Black Downs score of 9/31 for both trials, and the RCT by Lekmanov et al.; Jadad score of 2 and Black Downs score of 4/31. The study by Larsen et al. had a higher Jadad score of 3 but the Black and Downs score was only 17/31. The trial of Jordan et al. scored the highest with a Jadad score of 5 and a Black and Downs score of 27/31. As only 6 studies were retained, a funnel plot to assess publication bias could not be created.

Study, design	***Patients***	***Comperator***	***Intervention***	***Outcome parameters***	***Limitations***
Jordan I. et al. Clin Nutr. 2015 Glutamine effects on heat shock protein 70 and interleukines 6 and 10: Randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children (13).	101 patients (1 month -14 years) with severe sepsis or post major surgery	Standard PN (SPN)	Standard PN plus Glutamine 0.33g/kg/d (SPN + Gln)	High Heat Shock Protein-70 longer maintained in SPN + Gln. No difference in interleukin 6, interleukin 10	1) Surrogate endpoints
Larsen B. et al. JPEN J Parenteral Enteral Nutr. 2015;39:171-179 Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants (11).	32 patients (neonates 40 weeks +/- 2.2 weeks) post cardiac surgery	Standard group Intralipid®	Intervention group Lipoplus® (50% MCT, 40% LCT, 10% Fish oil)	Intervention group: Procalcitonin lower in at day 1, Leukotriene B4 higher at day 1 and 7, but lower at day 10. Lymphocyte concentration lower	1) Post hoc analysis 2) Underpowered to draw clinical conclusions 3) Intervention already started before surgery
Lekmanov A. et al.Anesteziol Reanimatol 2013; Jan-Feb;(1):49-51 Study of glutamine solution use efficiency in pediatric patients with heavy thermic burns and concomitant injuries in the intensive care unit (14).	40 patients (2-15 years old) with thermic burns	Standard PN	Standard PN plus glutamine (2 ml/kg)	Intervention group: shorter duration of mechanical ventilation. No differences in levels of protein, albumin or glutamine	1)No statistical analysis description 2) Methods inaccurately described 3) Glutamine levels not different between groups
Larsen B. et al. Clin Nutr. 2012 Jun;31(3):322-9 Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial (17).	32 patients (neonates 40 weeks +/- 2.2 weeks) post cardiac surgery	Standard group Intralipid®	Intervention group Lipoplus® (50% MCT, 40% LCT, 10% Fish oil)	Intervention group: TNF alpha plasma levels lower prior to and after surgery. Pro-inflammatory markers lower.	1) Surrogate endpoints 2) No clinical outcome difference 3) Intervention already started before surgery

Chaloupecky, V. et al. J Thorac Cardio-vasc Surg 1997;114:1053-60 Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support (10).	37 patients (2 months -1 year) post cardiac surgery	Standard group Glucose 10% 25 kcal/kg *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group Glucose 10-20% and amino acid 0.8 g/kg/d 33 kcal/kg *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group: Nitrogen balance less negative on day 1. Standard group: decrease in plasma levels of branched amino acids (valine, leucine, isoleucine), alanine, glycine and proline on day 2	1) Surrogate endpoints 2) Short intervention time
Chaloupecky, V. et al. Cor et Vasa 1994;36:26-34 The effect of early parenteral nutrition on amino acid and protein metabolism in infants following congenital heart disease surgery in extracorporeal circulation (12).	29 patients (6.5 months +/- 3 months) post cardiac surgery	Standard group Glucose 10% *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group Glucose 20% and amino acid 0.8 g/kg/d *Intervention only on day 1 postoperatively afterwards EN (no PN)*	PN group: Nitrogen balance less negative on day 1. Standard group: decrease in plasma levels of branched amino acids (valine, leucine, isoleucine), glutamine, arginine and proline on day 2	1) Surrogate endpoints 2) Short intervention time

Table 1: Overview of 5 RCT's and 1 post-hoc analysis identified as support of PN in critical ill children

Discussion

This systematic review could identify only 6 small RCTs that investigated the impact of a different dose or composition of PN in critically ill infants or children treated in the PICU. Of these 6 studies, 4 investigated infants after cardiac surgery and two included children with sepsis or after other major surgery, or burns respectively. The focus of these few studies was on intermediate or surrogate endpoints, such as nitrogen balances and inflammation markers, which appeared to be beneficially affected by providing more or altered parenteral nutrition early during critical illness. As the studies were small, all were statistically underpowered to detect a clinically relevant effect on patient-centered endpoints. Only the RCT by Lekmanov et al. reported a significant reduction of the duration of mechanical ventilation in children receiving glutamine-supplemented parenteral nutrition. However, with limited information on the used methodology which lacked a statistical analysis plan, the accuracy of these results cannot be determined. Hence, strong clinical conclusions cannot be drawn from these studies. As a result, no recommendations can be made regarding the optimal timing for initiation and composition of parenteral nutrition for use in critically ill infants and children.

The lack of large RCTs on the use of parenteral nutrition in critically ill infants and children is striking. However, this is an observation that is not limited to the nutritional field. Indeed, there are only 7 randomized controlled trials of PICU patients that have addressed a clinical question with a large enough sample size to be able to detect a difference in patient-centered, hard clinical outcomes (18-25), of which 3 are related to metabolic aspects (19, 20, 23). This overall lack of large RCTs in PICU patients suggests difficulties in recruiting large numbers of patients, due to the fact that the number of PICU patients and the size of the PICUs worldwide are smaller than for adult intensive care.

All the trials retained by the search strategy of this systematic review focused on surrogate endpoints, such as nitrogen balances and inflammation markers. This may hold some risks. Surrogate nutritional outcome measures are often used to describe mechanistic effects of an intervention. However, there is often a weak relationship, if any, between these surrogate endpoints and the important patient-centered

clinically relevant outcomes. Sometimes surrogate endpoints can be misleading as they may inadvertently suggest a benefit whereas the clinical outcomes indicate harm. For example, a large well-designed RCT of critically ill adults found that the administration of growth hormone, with the intention to improve anabolism and outcome, improved nitrogen balances but increased mortality (26). Also another large trial showed that early PN in adult ICU patients reduced markers of inflammation while it increased infections, weakness and organ failure and slowed down recovery (27). Surrogate outcome measures are also the main focus of limited pediatric studies on glutamine-supplemented parenteral nutrition, that failed to show any advantage in critically ill children, just as enteral supplementation of glutamine (28). Glutamine supplementation is no longer supported in adult critical care, based on the results of recent large high-quality RCTs that showed either no effect on morbidity or revealed and increased late mortality with glutamine supplementation (29-31).

In contrast to the PICU, there appears to be a greater consensus in the neonatal ICU, in favor of early parenteral supplementation. However, again the evidence generated by large RCTs with hard clinical endpoints is quite limited. In a Cochrane review, Trivedi et al (32) included 7 RCTs comparing the effect of intravenous early amino acid administration (within 24 hours after admission) with late initiation (>24 hours) in 394 low birth weight neonates on short-term in-hospital outcomes including mortality, early and late growth or neurodevelopment. There were no differences in length and occipitofrontal circumference, however nitrogen balance improved with early administration of amino acids. The impact on other outcomes was not reported. Only with early initiation of parenteral lipids, an improved neonatal growth has been suggested by two RCTs of very-low-birth-weight infants (33, 34).

In contrast with the pediatric critically ill patient population, recent large and high quality trials have provided more evidence to support nutritional recommendations for adult critically ill patients (27, 35-37). The EPaNIC (the impact of early parenteral nutrition completing enteral nutrition in adult critically ill patients trial) compared early parenteral supplementation of insufficient enteral feeding with tolerating the caloric deficit that accumulates when EN only is given in 4640 adult ICU patients (27). This study

found that not using PN during the first week in ICU resulted in fewer new infections, less ICU acquired weakness with earlier weaning from mechanical ventilation (38), less liver dysfunction(39) and reduced need for renal replacement therapy, together resulting in an earlier live discharge from the ICU and from the hospital (27). The SPN (the impact of supplemental parenteral nutrition on infection rate, duration of mechanical ventilation and rehabilitation in ICU patients) trial compared the initiation of PN on day 4, when adult patients were not yet receiving 60% of their caloric needs, with tolerating a nutritional deficit with EN until day 8 (37). The SPN trial showed no differences in the clinically relevant outcomes. The early Parenteral Nutrition trial investigated whether PN should be started very early in critically ill patients when there was a short-term relative contra-indication to EN and apart from a shorter duration of mechanical ventilation (which was a tertiary outcome measure) there were no other clinical benefits (36). The evidence generated from these trials has resulted in a change in clinical practice of adult intensive care, with a tendency to delay initiation of PN and to accept the macronutrient deficits for up to one week in ICU (40).

While the evidence from high quality RCTs no longer supports the early use of PN for critically ill adult patients, and while the literature may suggest the opposite for preterm newborns, there is currently no evidence to support any of the current PN practices for critically ill patients from term neonates to adolescents. Although several observational studies of large cohorts of critically children have shown a relation between the adequacy of feeding and of protein intake during the first 10 days of admission and lower risk of death (4, 41), the adult literature calls for caution in assuming that this association is causal. Hence, whether and for how long the substantial macronutrient deficit that accumulates in critically ill infants and children on enteral feeding only can be tolerated remains an open question. Further research is therefore necessary to address this question and to determine the role of PN in the PICU population. In order to answer this important question, the study should be large enough to have enough statistical power to detect relevant differences in hard clinical endpoints. The results of the currently ongoing multicenter randomized controlled PEPaNIC trial (Clinical Trials.gov NCT 01536275),

will hopefully elucidate some of the controversial topics. The PEPaNIC trial is a study of 1440 critically ill infants and children, and compares the effects of early PN with no PN for up to one week in PICU on several patient-centered clinical endpoints such as new infections and the duration of PICU dependency, besides safety endpoints including mortality (42).

References

1. Mehta NM, Compher C, Directors ASPENBo. A.S.P.E.N. Clinical Guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr. 2009 May-Jun;33(3):260-76.

2. Mehta NM, McAleer D, Hamilton S, Naples E, Leavitt K, Mitchell P, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. JPEN J Parenter Enteral Nutr. 2010 Jan-Feb;34(1):38-45.

3. Hulst J, Joosten K, Zimmermann L, Hop W, van Buuren S, Buller H, et al. Malnutrition in critically ill children: from admission to 6 months after discharge. Clin Nutr. 2004 Apr;23(2):223-32.

4. Mehta NM, Bechard LJ, Cahill N, Wang M, Day A, Duggan CP, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. Critical care medicine. 2012 Jul;40(7):2204-11.

5. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med. 2009 Sep 10;361(11):1088-97.

6. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R, Parenteral Nutrition Guidelines Working G, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). Journal of pediatric gastroenterology and nutrition. 2005 Nov;41 Suppl 2:S1-87.

7. Kerklaan D, Fivez T, Mehta NM, Mesotten D, van Rosmalen J, Hulst J, et al. Worldwide survey of nutritional practices in pediatric intensive care units. Pediatr Crit Care Med 2016 *In press*.

8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996 Feb;17(1):1-12.

9. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. Journal of epidemiology and community health. 1998 Jun;52(6):377-84.

10. Chaloupecky V, Hucin B, Tlaskal T, Kostelka M, Kucera V, Janousek J, et al. Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support. J Thorac Cardiovasc Surg. 1997 Dec;114(6):1053-60.

11. Larsen BM, Field CJ, Leong AY, Goonewardene LA, Van Aerde JE, Joffe AR, et al. Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants. JPEN J Parenter Enteral Nutr. 2015 Feb;39(2):171-9.

12. Chaloupecky V, Vislocky, I.,Pachl, J.,Sprongl, L.,Svomova, V. The effect of early parenteral nutrition on amino acid and protein metabolism in infants following congenital heart disease surgery in extracorporeal circulation. Cor et Vasa. 1994;36(1):26-34.

13. Jordan I, Balaguer M, Esteban ME, Cambra FJ, Felipe A, Hernandez L, et al. Glutamine effects on heat shock protein 70 and interleukines 6 and 10: Randomized trial of glutamine supplementation versus standard parenteral nutrition in critically ill children. Clin Nutr. 2015 Feb 7.

14. Lekmanov AU, Erpuleva, U. V.,Zolkina, I. V.,Rossaus, P. A. [Study of glutamine solution use efficiency in pediatric patients with heavy thermic burns and concomitant injuries in the intensive care unit]. Anesteziologiia i reanimatologiia. 2013 Jan-Feb(1):49-51.

15. Alexander JW, MacMillan BG, Stinnett JD, Ogle CK, Bozian RC, Fischer JE, et al. Beneficial effects of aggressive protein feeding in severely burned children. Ann Surg. 1980;192(4):505-17.

16. Larsen BM, Goonewardene, L. A.,Field, C. J.,Joffe, A. R.,Van Aerde, J. E.,Olstad, D. L.,Clandinin, M. T. Low energy intakes are associated with adverse outcomes in infants after open heart surgery. JPEN J Parenter Enteral Nutr. 2013 Mar;37(2):254-60.

17. Larsen BM, Goonewardene, L. A.,Joffe, A. R.,Van Aerde, J. E.,Field, C. J.,Olstad, D. L.,Clandinin, M. T. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. Clin Nutr. 2012 Jun;31(3):322-9.

18. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011 Jun 30;364(26):2483-95.

19. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009 Feb 14;373(9663):547-56.

20. Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, et al. A randomized trial of hyperglycemic control in pediatric intensive care. N Engl J Med. 2014 Jan 9;370(2):107-18.

21. Lacroix J, Hebert PC, Hutchison JS, Hume HA, Tucci M, Ducruet T, et al. Transfusion strategies for patients in pediatric intensive care units. N Engl J Med. 2007 Apr 19;356(16):1609-19.

22. Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. N Engl J Med. 2010 May 27;362(21):1980-92.

23. Agus MS, Steil GM, Wypij D, Costello JM, Laussen PC, Langer M, et al. Tight glycemic control versus standard care after pediatric cardiac surgery. N Engl J Med 2012 Sep 27;367(13):1208-19.

24. Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation. 2003 Feb 25;107(7):996-1002.

25. Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, et al. Hypothermia therapy after traumatic brain injury in children. N Engl J Med. 2008 Jun 5;358(23):2447-56.

26. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med 1999 Sep 9;341(11):785-92.

27. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011 Aug 11;365(6):506-17.

28. Briassouli E, Briassoulis G. Glutamine randomized studies in early life: the unsolved riddle of experimental and clinical studies. Clin Dev Immunol. 2012;2012:749189.

29. Heyland D, Muscedere J, Wischmeyer PE, Cook D, Jones G, Albert M, et al. A randomized trial of glutamine and antioxidants in critically ill patients. N Engl J Med. 2013 Apr 18;368(16):1489-97.

30. van Zanten AR, Hofman Z, Heyland DK. Consequences of the REDOXS and METAPLUS Trials: The End of an Era of Glutamine and Antioxidant Supplementation for Critically Ill Patients? JPEN J Parenter Enteral Nutr. 2015 Jan 7.

31. Tao KM, Li XQ, Yang LQ, Yu WF, Lu ZJ, Sun YM, et al. Glutamine supplementation for critically ill adults. Cochrane Database Syst Rev. 2014;9:CD010050.

32. Trivedi A, Sinn JK. Early versus late administration of amino acids in preterm infants receiving parenteral nutrition. Cochrane Database Syst Rev. 2013;7:CD008771.

33. Drenckpohl D, McConnell C, Gaffney S, Niehaus M, Macwan KS. Randomized trial of very low birth weight infants receiving higher rates of infusion of intravenous fat emulsions during the first week of life. Pediatrics. 2008 Oct;122(4):743-51.

34. Fischer CJ, Maucort-Boulch D, Essomo Megnier-Mbo CM, Remontet L, Claris O. Early parenteral lipids and growth velocity in extremely-low-birth-weight infants. Clin Nutr. 2014 Jun;33(3):502-8.

35. Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. N Engl J Med. 2014 Mar 27;370(13):1227-36.

36. Doig GS, Simpson F, Early PNTIG. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a full economic analysis of a multicenter randomized controlled trial based on US costs. ClinicoEconomics and outcomes research : CEOR. 2013;5:369-79.

37. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013 Feb 2;381(9864):385-93.

38. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013 Oct;1(8):621-9.

39. Vanwijngaerden YM, Langouche L, Brunner R, Debaveye Y, Gielen M, Casaer M, et al. Withholding parenteral nutrition during critical illness increases plasma bilirubin but lowers the incidence of biliary sludge. Hepatology. 2014 Jul;60(1):202-10.

40. Vincent JL, Preiser JC. When should we add parenteral to enteral nutrition? Lancet. 2013 Feb 2;381(9864):354-5.

41. Mehta NM, Bechard LJ, Zurakowski D, Duggan CP, Heyland DK. Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study. Am J Clin Nutr. 2015 Jul;102(1):199-206.

42. Fivez T, Kerklaan D, Verbruggen S, Vanhorebeek I, Verstraete S, Tibboel D, et al. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. Trials. 2015;16:202.

4. Worldwide survey of nutritional practices in pediatric intensive care units

Adapted from:

Kerklaan D, Fivez T*, Mehta NM, van Rosmaelen J, Hulst JM, Van den Berghe G, Joosten KF, Verbruggen SC. Worldwide Survey of Nutritional Practices in PICUs. Pediatr Crit Care Med. 2016 Jan; 17 (1):10-8*

** Equal contribution*

Abstract

Objective

To assess current nutritional practices in critically ill children worldwide.

Design

A two-part online, international survey. The first part, the *survey,* was composed of 59 questions regarding nutritional strategies and protocols (July-November 2013). The second part surveyed the *point-prevalence* of nutritional data of patients present in a subgroup of the responding PICUs (May-September 2014).

Setting

Members of the World Federation of Pediatric Intensive and Critical Care Societies were asked to complete the survey.

Subjects

Pediatric critical care providers.

Interventions

Survey.

Measurements and Main Results

We analyzed 189 responses from 156 PICUs in 52 countries (*survey*). We received nutritional data on 295 patients from 41 of these 156 responding PICUs in 27 countries (*point-prevalence*). According to the *survey*, nutritional protocols and support teams were available in 52% and 57% of the PICUs, respectively. Various equations were in use to estimate energy requirements; only in 14% of PICUs indirect calorimetry was used. Nutritional targets for macronutrients, corrected for age/weight, varied widely. Enteral nutrition (EN) would be started early (within 24 hours of admission) in 60% of PICUs; preferably by the gastric route (88%). In patients intolerant to EN, parenteral nutrition (PN) would be started within 48 hours in 55% of PICUs. Overall, in 72% of PICUs supplemental PN would be used if EN failed to meet at least 50% of energy delivery goal.

Several differences between the intended (*survey*) and the actual (*point prevalence*) nutritional practices were found in the responding PICUs, predominantly overestimating the ability to adequately feed patients.

Conclusion

Nutritional practices vary widely between PICUs worldwide. There are significant differences in macronutrient goals, estimating energy requirements, timing of nutrient delivery, and threshold for supplemental PN. Uniform consensus-based nutrition practices, preferably guided by evidence, are desirable in the PICU.

Keywords (max 6): Pediatric; intensive care units; nutritional support; parenteral nutrition; enteral nutrition; questionnaires

Introduction

Nutritional support affects recovery and outcome in critically ill children [1-3]. Although undernutrition has been the primary focus, overfeeding in Pediatric Intensive Care Units (PICUs) is also associated with increased morbidity [4, 5]. Despite its clinical relevance, there is a scarcity of high-level evidence on various aspects of nutritional support in critically ill children [6]. With grade C as the maximum level of evidence, available guidelines for nutrition support in critically ill children are based on insufficient data for evidence-based recommendations.

Consensus-based guidelines provided by expert committees (American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)) are based on scant evidence, and are largely driven by expert opinion and extrapolations from studies in adults or non-critically ill children [7, 8]. Low-grade or inconclusive evidence-based protocols represents a barrier to implementation with differences most prominent in areas with the weakest evidence [9, 10]. This allows wide variations in nutritional practices for patients in European PICUs as shown in previous studies [11, 12]. The variability in timing, amount and composition of nutrition would inevitably result in underfeeding and/or overfeeding, which could potentially impact the clinical outcome of critically ill children and overall health care expenses [13]. While evidence on many aspects of nutrition is lacking, there appears to be consensus on the benefits of early enteral nutrition (EN) and need to prevent further nutritional deterioration in this population.

The purpose of our study was to assess the current nutritional practice in PICUs across the world. We hypothesized that the limited guidelines available have not been universally implemented, and that current practice is heterogeneous and mostly physician based. Since the guidelines at least agree on the importance of EN [7, 14, 15], we expected no significant differences in this practice between PICUs. Other factors, such as assessment of energy requirements or use of parenteral nutrition (PN), are more likely to vary between countries and hospitals given the weak recommendations.

To quantify the variations in clinical practice, we distributed a two-part online survey to PICUs across the world. The first part of the *survey* was composed of questions on various aspects of local nutritional practice. The second part was a *point-prevalence* survey on nutritional data collected in all patients present in the unit on a single day in a subgroup of the responding PICUs. Answers were analyzed, correlated with PICU characteristics and differences between the intended (*survey*) and the actual (*point prevalence*) nutritional practices were determined.

Material and Methods

The local Institutional Review Board of the Erasmus MC in Rotterdam waived the need for consent. The participation in this survey was voluntary and no patient identifiers were collected.

The cross-sectional *survey* was conducted between July and November 2013. The online questionnaire was composed of 59 questions regarding local nutritional protocols and strategies, and provided in English, French, Spanish and Chinese. The second part, the *point-prevalence*, conducted between May and September 2014, involved data collection on nutritional practices and intake for the preceding 24 hours. In a subgroup of centers that agreed to participate in this portion of the study, respondents were asked to include data for all patients present in their PICU; no selection criteria were applied. Both questionnaires are available as an online digital supplement.

Testing of clarity, relevance and clinical sensibility of the English questionnaire was performed by independent clinicians in three centers (Sophia Children's Hospital-Erasmus MC, Rotterdam, the Netherlands; University Hospital of Leuven, Belgium; and the Boston Children's Hospital, U.S.A.). Data from this test were not included in the final analysis and survey results. Afterwards, the questions were translated to French, Spanish and Chinese by native speakers.

An invitation to the *survey* was electronically distributed to members of the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS) by their mailing list and to specific members of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) and Society of Critical Care

Medicine (SCCM) involved in nutritional management, and through the newsletter of both the ESPNIC and WFPICCS and the WFPICCS homepage and LinkedIn group. A reminder was sent 2 months after the first invitation. Due to incomplete data registration, the exact number of PICUs represented by the WFPICCS database is unknown. Respondents that provided their contact information in the *survey,* were approached to participate in the *point-prevalence*.

If more than one questionnaire was returned from a single PICU, the answers were weighted by the inverse of the number of completed questionnaires per center, in order to process conflicting statements within a single institution without disrupting the weight of the answers per PICU. Countries were classified by income according to The World Bank income groups [16]. Individual questions were stratified by continent, income of country, number of PICU beds, admissions per year and percentage of ventilated patients.

Statistical analysis was performed using IBM SPSS statistics 21 for Windows (IBM, Chicago IL, USA). Descriptive statistics were used to compare differences in respondent characteristics and survey responses. Nutritional data obtained in the *point-prevalence,* were compared to the *survey* results for each participating center. Logistic regression, ordinal or multinomial, depending on the type of outcome, was used to identify the relation between the answers provided and the characteristics of the different PICUs. To correct for cluster effects due to multiple returned questionnaires per PICU, generalized estimating equations were used in conjunction with robust standard error estimates (Huber sandwich estimator). All statistical tests were two-sided and statistical significance was defined as a P-value < 0.05.

This trial was registered in the Dutch Trial Register (NTR) at number 4093 (www.trialregister.nl).

Results

Response

After distribution of the first part of the *survey* a total of 251 questionnaires were received. Fifty-two questionnaires were removed because of missing essential data, defined as nutritional data (so only information on PICU characteristics available) and/or data essential for distinguishing PICUs from each other without possibility for clarification. Of the remaining 199 questionnaires, 10 were duplicate replies by the same respondent and therefore deleted. 189 questionnaires were analyzed, representing 156 PICUs in 52 countries and 6 continents as shown in Figure 1.

For the *point-prevalence* we collected nutritional data on 295 patients in total, from 41 of the responding PICUs (26%) from 27 countries on 6 continents with a median input of 5 patients (IQR 2-9) per PICU. Characteristics of responding PICUs for the *point-prevalence* were similar compared to the overall *survey* respondents (Table 1).

PICU and patient demographics

The responding PICUs in the first part of the *survey* represented approximately 90,000 admissions per year. Fifty-two percent of PICUs were located in North-America and Europe. Fourteen percent of PICUs were situated in low or lower middle income countries and 86% of PICUs were multidisciplinary. All PICU demographics are shown in Table 1.

Of the 295 patients included in the *point-prevalence*, 60% was male and 58% younger than 1 year. Median length of stay (LOS) at moment of data collection was 6 days (IQR 2-15), with a LOS greater than 7 days in 40% of the patients. Median weight was 7 kg (IQR 4-16) and 46% of the children were mechanically ventilated.

Nutritional support

According to the first part of the *survey*, a nutritional protocol was present in 52% of PICUs; protocol characteristics are shown in Table 2. A Nutrition Support Team (NST) was available in 57% of the

PICUs and 51% of the teams visited the ICU daily. The composition of an NST differed; it consisted mostly of dieticians (88%) and pediatric intensivists (51%).

In the *point prevalence part of the study*, median caloric intake did not differ in children fed by EN exclusively (n=129) between the following four groups (p=0.18); 1. PICUs with an NST (76 kcal/kg/day), 2. PICUs with a nutritional protocol (76 kcal/kg/day), 3. PICUs with both an NST and nutritional protocol (64 kcal/kg/day,) 4. PICUs without an NST and protocol (58 kcal/kg/day).There was also no difference in the proportion of children receiving EN in PICUs with and without an NST and/or protocol.

Nutritional requirements

To predict energy expenditure (EE) different equations were used according to the first part of the *survey*, mainly those published by Schofield (25%) and the WHO (25%), but also the Harris-Benedict equation (17%) [17-19]. Seventy percent used correction factors, as fever (41% of PICUs), diagnosis (54%) and growth (23%) to calculate energy needs. Twenty-four percent of respondents did not know which equation was used to calculate EE in their unit. Indirect calorimetry (IC) to measure EE was used in 14% of the PICUs. The first IC measurement was performed if expected stay was longer than 4 days (31% of PICUs), as soon as ventilator settings were appropriate (18%), in case of weight loss (15%) or patient dependent (11%: obese patients, high risk of malnutrition).

Age based-protein targets recommended by the A.S.P.E.N. and ESPEN/ESPGHAN guidelines (ranging from 0.9 to 3 g protein/kg/day) were followed in 31% and 36% of PICUs, respectively [7, 8]. Lipid targets ranged from < 1.5 to > 3.5 g/kg/day; where the range of 1.5 to 2.5 g/kg/day was predominantly used (41%). Sixteen percent and 7.9% of the respondents did not know what their protein and lipid targets were, respectively.

In the *point-prevalence*, median caloric intake was 66 kcal/kg/day (IQR 49-96) for children on EN exclusively (n=129); intake per kg of weight decreased significantly with age as expected (p<0.001, Fig. 2). In 31% of the children the caloric intake was lower than basal metabolic rate calculated by the weight-based Schofield equation; for the WHO equation this was 27%. Median protein intake was 1.8

g/kg/day (IQR 1.2-2.6); only 34% of the children met the intended target protein intake of their PICU as mentioned in the *survey*.

Timing and route of nutrition

In the first part of the *survey*, an early start (within 24 hours after admission) of EN was mentioned for 60% of PICUs; in 31% EN would even be started within 12 hours (Fig. 3). Fifty-nine percent of the respondents had the perception that they were able to feed patients exclusively by enteral route within 3 days post-admission. The gastric route was preferred for EN in ventilated (67% of PICUs) and non-ventilated patients (88%). Pro-kinetics were prescribed when a patient was not tolerating feeds in 70% of PICUs. EN was stopped or decreased due to the following reasons: high gastric residuals (73% of PICUs), abdominal distension/pain (85%), diarrhea (32%), vomiting (75%), reduced/altered bowel sounds (23%), hemodynamic instability (62%) or use of muscle relaxants (12%).

Early PN would be started within 48 hours after admission in 55% of PICUs, while in 3.5% of PICUs there would be trials of EN for of at least 7 days before starting PN (Fig. 3). When EN was insufficient, respondents from 18% of the PICUs would always supplement PN, whereas in 7.5% supplemental PN would never be utilized. Seventy-two percent supplemented PN if EN failed to meet 50% of target calories; 24% if EN failed to meet 80%. PN was stopped in 64% of PICUs when EN covered > 80% of the nutritional targets.

At the moment of our *point-prevalence* 73% of the children received EN (n=216), predominantly by gastric tube (70%). There was no difference in caloric intake (p=0.82) or in pro-kinetics use (p=0.47) between children fed by gastric or post-pyloric route. Forty-two percent of children with LOS < 24 hours (n=43) were already receiving EN and in children with LOS of 2 days or more (n= 253), EN was provided in 78%. Twenty-one percent of all children received PN in some form and 10% received a combination of EN and PN; both groups at a median LOS of 6.5 days. The *point-prevalence* showed that the ability to administer exclusive EN was overestimated; 40% of children (n=74) present during the

point-prevalence achieved exclusive EN later than perceived by the respondents from the first part of the survey.

Glucose and glycemic control

In the first part of the *survey*, target intake of glucose during the first 12-24 hours of admission varied between < 2 to > 6 mg/kg/min for different weight ranges (Fig. 4). In 62% of the PICUs a protocol for some form of glycemic control was available. Target blood glucoses were defined as < 10 mmol/L (<180 mg/dL), in 54%, and < 8 mmol/L (< 144 mg/dL) in 23%. Tight glucose control (2.8-4.4 mmol/L or 50-80 mg/dL < 1 year or 3.9-5.5 mmol/L or 70-100 mg/dL 1-16 years) as reported by Vlasselaers et al [20] was practiced in 10% of PICUs.

At the time of the *point-prevalence*, 20 children, median weight 8.1 kg, received exclusive glucose infusion while being admitted < 24 hours; median glucose intake was 1.7 mg/kg/min (IQR 0.3-2.3). Seventy-five percent received less glucose than their target glucose intake (Fig. 4).

Insulin was administered in 32 children (11%); 24 children on insulin were admitted to a PICU with a glucose target < 10 mmol/L (<180 mg/dL), five to a PICU that practiced tight glucose control as reported by Vlasselaers et al [20].

Administration of parenteral lipids and protein

According to the first part of the *survey*, lipids were supplied in different compositions (Table 3). In 44% of PICUs a step-up protocol was used that would start at 50% of the maximal dose. Lipid intake was decreased when triglycerides were 3.5-5.5 mmol/L or 310-487 mg/dL (in 69%) and stopped when triglycerides exceeded 5 mmol/L or 442 mg/dL (in 70%). In case of sepsis, lipid administration was decreased or stopped in 50% of PICUs. Reasons provided to decrease or stop the intake of protein were kidney failure (65%) and urea levels >15 mmol/L or 42 mg/dL (75%).

Geographic and socioeconomic differences

An NST was more often available in PICUs situated in North America (p=0.014), South America (p=0.005) and Oceania (p=0.013) than in Europe, and in PICUs with more admissions per year

(p=0.029). A higher percentage of nutritional protocols (p=0.006) and support teams (p<0.001) were available in high-income countries than low-middle ones. As expected, protein targets in North American PICUs were more often based on A.S.P.E.N. (p=0.011) and less frequently on ESPEN/ESPGHAN guidelines (p<0.001) than protein targets in Europe. EN was started earlier in PICUs in high-income countries (mean 6-24 hours; 81% within 24 hours) than in lower-middle-income countries (mean 13-48 hours; 74% within 24 hours, p=0.012). PN was started later in PICUs in North America (median 2-4 days, p=0.02) and Asia (median 2-4 days, p=0.06) than in PICUs in Europe (median < 48 hours) in a child intolerable to enteral feeds. An overview of the adjusted Odds Ratios per continent is provided in Supplemental Digital Content - Table 1.

Discussion

Nutritional practices vary greatly between PICUs worldwide. Several aspects of nutritional support differ significantly; such as macronutrient goals, preferred route and timing, estimation of energy requirements, and the threshold for supplemental PN use. These differences were apparent between PICUs in general, and between geographic and socioeconomic regions. Many of these areas currently lack evidence. This variability has been described before in PICUs in several European countries [11, 12]. In addition, applied nutritional practice (*point-prevalence*) deviates from local protocols or strategies (*survey)* on multiple occasions, increasing the variation of clinical nutritional practice even more. Similar results were recently shown by Martinez et al, describing nutritional practices by detailed prospective data collection in 524 mechanically ventilated patients from 31 international PICUs [21]. They found a wide variation in EN recommendations not in agreement with national guidelines.

Variation in practice was not only observed between PICUs in our current study; we also received conflicting statements within single institutions. We corrected for this issue, by weighting by the inverse of the number of completed questionnaires per center. The conflicting statements underline the observed variation of nutritional practices, which occurs not only between but also within individual

institutions. A similar discordance in practice within institutions was reported in a UK survey of glycemic control in PICUs [22].

Globally, guidelines for nutritional support have been released by nutritional organizations. The American (A.S.P.E.N). and European (ESPEN/ESPGHAN) societies provide specific guidelines for nutrition in critically ill children [7, 8]. However, they do not advise on every aspect of nutritional support. Agreements and differences between these guidelines and current practice, as shown by our survey, are summarized in Supplemental Digital Content - Table 2.

Overall, the most striking similarity between guidelines and local implementation is the preference for EN as the preferred route of nutrient delivery and its early initiation in critically ill children.

A specialized NST and feeding protocols are recommended by the A.S.P.E.N guidelines for critically ill children [7]. Availability of an EN protocol is associated with a lower prevalence of hospital-acquired infections [3], implementation of an NST with an increase in EN use and decreased reliance on PN [23]. Our *survey* showed that a nutritional protocol and/or NST were available in approximately half the PICUs. In our *point prevalence* we found no significant difference in caloric intake and use of EN between patients from centers with and without protocol. However, since this was a secondary analysis, it cannot prove or disprove the utility of NST/protocols in general. In single centers, a stepwise EN algorithm has been shown to significantly improve the timing of EN initiation and the ability to reach nutrient delivery goals [24, 25]. The role of protocols and NSTs in optimizing clinical outcomes in the PICU population needs to be further examined in well-designed trials.

The ESPEN/ESPGHAN guidelines prefer the measurement of REE to the use of equations. The A.S.P.E.N. guidelines recommend targeted use of indirect calorimetry (IC) in a select group of patients with suspected metabolic alterations or malnutrition. Both state that in the absence of IC, reasonable values can also be derived from formulas, e.g. Schofield, but only when applied without the use of universal correction factors [7, 8]. Several other sources state that nutritional therapy should be targeted

at REE throughout the course of illness [26, 27]. However, due to the limited availability and practice of IC [11], and also to inaccurate predictive equations [26-28], it is difficult to assess REE in critically ill children. Use of the WHO and Schofield equations, most commonly used to determine requirements, may lead to underfeeding and overfeeding and potentially impact morbidity and mortality [3, 4]. We confirmed the finding of previous studies [11] that IC to measure REE is used in a small minority of European (20%) and worldwide (14%) PICUs. In contrast with both guidelines, energy needs were calculated with use of correction factors in the majority of PICUs in absence of IC. In the *point-prevalence* 2/3 of the children on exclusive EN received more calories than BMR calculated by the Schofield or WHO formula.

Timing of nutrition is not widely covered by the pediatric ESPEN/ESPGHAN and A.S.P.E.N. guidelines. The adult guidelines from the same societies agree on the importance of early EN but contain contradictory recommendations regarding PN [14, 15, 29]. The importance and benefits of early EN are generally accepted in previous studies in adults and children [1, 30-33], and in critically ill children a higher intake by enteral route is associated with a lower 60-days mortality [3]. In our *survey* as well as in the *point-prevalence* EN was initiated early; within 24 hours after admission to the PICU. Overall, characteristics of EN support were quite similar between PICUs, with a preference for the gastric route. Also PN was started early; within 48 hours. The mentioned difference in PN initiation time between Europe and North America could reflect the contradictory recommendations in adult guidelines in these regions, which agree on the importance of early EN but not on the time at which supplemental PN should be started [15, 29]. The optimal timing and dose of PN is still under debate [34]. We are currently conducting a trial comparing early versus late supplemental PN in critically ill children who are intolerant of EN (ClinicalTrials.gov: NCT 01536275), which is expected to complete enrolment by the end of 2015.

Prospective data from PICUs on patients receiving EN show that only 38-86% of energy goals were administered via this route [5, 35]. A variety of barriers impede EN delivery in the PICU setting [36, 37].

Only 60% of the patients of the *point-prevalence* were actually on exclusive EN within the time frame mentioned in the *survey*. Although post-pyloric feeding might improve caloric intake [38], most patients evaluated in our *survey* and *point-prevalence* were fed by the gastric route with no difference in nutrient intake compared to children fed via the post-pyloric route (*point-prevalence)*. The time to feed patients exclusively by the enteral route was short; 59% of respondents thought their PICU was able to feed their patients within 3 days, but this time was overestimated.

Glucose targets in the ESPEN/ESPGHAN pediatric guidelines are supported by limited evidence; A.S.P.E.N does not provide recommendations on macronutrient intake due to insufficient data. In our *survey* glucose intake targets during the first 12-24 hours tended to range between 2-6 mg/kg/min and decreased with increasing weight. The upper limit of glucose intake for critically ill children according to ESPEN/ESPGHAN (5 mg/kg/min, based on the maximal oxidation rate) was exceeded by more than 7% of PICUs. Our *point prevalence* showed that in 75% of the patients glucose intake differed from the glucose targets mentioned in the first part of the survey. However, we should be very careful to draw conclusions from that number, because only 20 children received glucose infusion exclusively during the first 24 hours of admission.

Target blood glucose levels varied between tight control [20] and a target glucose < 10 mmol/L or 180 mg/dL. This discrepancy in definitions and implementation in glucose management has been highlighted before [39, 40]. The discrepancy in definitions and implementation stems from the fact that uncertainties about risks and benefits remain [20, 41]. A recent UK trial showed no benefit [42] and another trial in North America is underway.

The strength of our study is the fact that we surveyed the local nutritional strategies as well as their implementation in clinical practice. Furthermore, to our knowledge, it is the first study to describe the practices in relation to income-characteristics of countries in 6 continents.

However, our survey may not provide accurate representations of these geographic regions. No response rate can be calculated, since the exact number of PICUs represented by WFPICCS is unknown. The total number of PICUs in all countries joined in the WFPICCS, as identified in the literature, is at least 969, so our 156 PICUs represent a small proportion of all PICUs worldwide. Our point prevalence data represent a small fraction of children in the PICUs per center as well as in the cohort invited to participate. The smaller number of PICUs in the point-prevalence study may have caused an aggravation of the selection bias, since it is possible that we mainly received point-prevalence data from PICUs with a strict protocol adherence. Hence, observations may not depict actual practices in these centers. However, characteristics of responding PICUs for the *point-prevalence* were similar compared to the overall *survey* respondents (table 1). Furthermore, many physicians have limited knowledge of nutritional practices in their centers. Our study may also be limited by the possibility that non-respondents of this survey were less interested in nutritional practices leading to a selection-bias and possible distorted reflection. On the other hand, this selection-bias may strengthen our conclusion, if even in the nutrition-minded respondents, adherence to available guidelines is limited. Finally, the heterogeneity of the PICU population may have caused some difficulties; many of the questions required an unambiguous answer, so only most applicable answers were provided. And, as feeding practices differ between populations, answers from combined PICUs (with neonates or adults; respectively 20 and 6% of the responding PICUs in this study) may falsely increase the perception of variability.

Nevertheless, our survey clearly demonstrates the international variation in nutritional practice in critically ill children and the differences due to the limited available guidelines; especially on macronutrient administration and calculation of energy targets. Evidence-based guidelines are needed, but are challenging to develop due to a heterogeneous PICU population. Guidelines can be either very specific in respect to disease and settings, leading to wide variation of practice, or be generally applicable with risk of being unfocused and therefore irrelevant in specific situations.

Conclusion

In terms of requirements, timing and route, nutritional practices among critically ill children vary greatly between PICUs worldwide. Even the limited available guidelines are not consistently followed and high-level evidence is urgently needed.

References

1. Briassoulis G, Zavras N, Hatzis T: Malnutrition, nutritional indices, and early enteral feeding in critically ill children. *Nutrition* 2001, 17(7-8):548-557.
2. Pollack MM, Ruttimann UE, Wiley JS: Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. *JPEN J Parenter Enteral Nutr* 1985, 9(3):309-313.
3. Mehta NM, Bechard LJ, Cahill N, Wang M, Day A, Duggan CP, Heyland DK: Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. *Crit Care Med* 2012, 40(7):2204-2211.
4. Chwals WJ: Overfeeding the critically ill child: fact or fantasy? *New Horiz* 1994, 2(2):147-155.
5. Mehta NM, Bechard LJ, Dolan M, Ariagno K, Jiang H, Duggan C: Energy imbalance and the risk of overfeeding in critically ill children. *Pediatr Crit Care Med* 2011, 12(4):398-405.
6. Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, Hartling L: Nutritional support for critically ill children. *Cochrane Database Syst Rev* 2009(2):CD005144.
7. Mehta NM, Compher C, Directors ASPENBo: A.S.P.E.N. Clinical Guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr* 2009, 33(3):260-276.
8. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R, Parenteral Nutrition Guidelines Working G, European Society for Clinical N, Metabolism, European Society of Paediatric Gastroenterology H, Nutrition *et al*: 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of

Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr* 2005, 41 Suppl 2:S1-87.

9. Bell MJ, Adelson PD, Hutchison JS, Kochanek PM, Tasker RC, Vavilala MS, Beers SR, Fabio A, Kelsey SF, Wisniewski SR *et al*: Differences in medical therapy goals for children with severe traumatic brain injury-an international study. *Pediatr Crit Care Med* 2013, 14(8):811-818.
10. Russ SJ, Sevdalis N, Moorthy K, Mayer EK, Rout S, Caris J, Mansell J, Davies R, Vincent C, Darzi A: A Qualitative Evaluation of the Barriers and Facilitators Toward Implementation of the WHO Surgical Safety Checklist Across Hospitals in England: Lessons From the "Surgical Checklist Implementation Project". *Ann Surg* 2014.
11. van der Kuip M, Oosterveld MJ, van Bokhorst-de van der Schueren MA, de Meer K, Lafeber HN, Gemke RJ: Nutritional support in 111 pediatric intensive care units: a European survey. *Intensive Care Med* 2004, 30(9):1807-1813.
12. Sharifi MN, Walton A, Chakrabarty G, Rahman T, Neild P, Poullis A: Nutrition support in intensive care units in England: a snapshot of present practice. *Br J Nutr* 2011, 106(8):1240-1244.
13. Correia MI, Waitzberg DL: The impact of malnutrition on morbidity, mortality, length of hospital stay and costs evaluated through a multivariate model analysis. *Clin Nutr* 2003, 22(3):235-239.
14. Kreymann KG, Berger MM, Deutz NE, Hiesmayr M, Jolliet P, Kazandjiev G, Nitenberg G, van den Berghe G, Wernerman J, Dgem *et al*: ESPEN Guidelines on Enteral Nutrition: Intensive care. *Clin Nutr* 2006, 25(2):210-223.
15. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G, Directors ASPENBo *et al*: Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine

(SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2009, 33(3):277-316.

16. The World Bank: Country classifications - country and lending groups. In.: The World Bank; 2014.

17. Schofield WN: Predicting basal metabolic rate, new standards and review of previous work. *Hum Nutr Clin Nutr* 1985, 39 Suppl 1:5-41.

18. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. *World Health Organ Tech Rep Ser* 1985, 724:1-206.

19. Harris JA, Benedict FG: A Biometric Study of Human Basal Metabolism. *Proc Natl Acad Sci U S A* 1918, 4(12):370-373.

20. Vlasselaers D, Milants I, Desmet L, Wouters PJ, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C *et al*: Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. *Lancet* 2009, 373(9663):547-556.

21. Martinez EE, Bechard LJ, Mehta NM: Nutrition algorithms and bedside nutrient delivery practices in pediatric intensive care units: an international multicenter cohort study. *Nutr Clin Pract* 2014, 29(3):360-367.

22. Nayak P, Lang H, Parslow R, Davies P, Morris K, Group UKPICSS: Hyperglycemia and insulin therapy in the critically ill child. *Pediatr Crit Care Med* 2009, 10(3):303-305.

23. Gurgueira GL, Leite HP, Taddei JA, de Carvalho WB: Outcomes in a pediatric intensive care unit before and after the implementation of a nutrition support team. *JPEN J Parenter Enteral Nutr* 2005, 29(3):176-185.

24. Meyer R, Harrison S, Sargent S, Ramnarayan P, Habibi P, Labadarios D: The impact of enteral feeding protocols on nutritional support in critically ill children. *J Hum Nutr Diet* 2009, 22(5):428-436.

25. Hamilton S, McAleer DM, Ariagno K, Barrett M, Stenquist N, Duggan CP, Mehta NM: A stepwise enteral nutrition algorithm for critically ill children helps achieve nutrient delivery goals*. *Pediatr Crit Care Med* 2014, 15(7):583-589.

26. Vazquez Martinez JL, Martinez-Romillo PD, Diez Sebastian J, Ruza Tarrio F: Predicted versus measured energy expenditure by continuous, online indirect calorimetry in ventilated, critically ill children during the early postinjury period. *Pediatr Crit Care Med* 2004, 5(1):19-27.

27. Framson CM, LeLeiko NS, Dallal GE, Roubenoff R, Snelling LK, Dwyer JT: Energy expenditure in critically ill children. *Pediatr Crit Care Med* 2007, 8(3):264-267.

28. Briassoulis G, Venkataraman S, Thompson AE: Energy expenditure in critically ill children. *Crit Care Med* 2000, 28(4):1166-1172.

29. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C *et al*: ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr* 2009, 28(4):387-400.

30. McClave SA, Martindale RG, Rice TW, Heyland DK: Feeding the Critically Ill Patient. *Crit Care Med* 2014.

31. Mikhailov TA, Kuhn EM, Manzi J, Christensen M, Collins M, Brown AM, Dechert R, Scanlon MC, Wakeham MK, Goday PS: Early Enteral Nutrition Is Associated With Lower Mortality in Critically Ill Children. *JPEN J Parenter Enteral Nutr* 2014.

32. Gramlich L, Kichian K, Pinilla J, Rodych NJ, Dhaliwal R, Heyland DK: Does enteral nutrition compared to parenteral nutrition result in better outcomes in critically ill adult patients? A systematic review of the literature. *Nutrition* 2004, 20(10):843-848.

33. Doig GS, Heighes PT, Simpson F, Sweetman EA, Davies AR: Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Med* 2009, 35(12):2018-2027.

34. Casaer MP, Van den Berghe G: Nutrition in the acute phase of critical illness. *N Engl J Med* 2014, 370(13):1227-1236.

35. de Betue CT, van Steenselen WN, Hulst JM, Olieman JF, Augustus M, Mohd Din SH, Verbruggen SC, Tibboel D, Joosten KF: Achieving energy goals at day 4 after admission in critically ill children; predictive for outcome? *Clin Nutr* 2014.

36. Mehta NM, McAleer D, Hamilton S, Naples E, Leavitt K, Mitchell P, Duggan C: Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. *JPEN J Parenter Enteral Nutr* 2010, 34(1):38-45.

37. Leong AY, Cartwright KR, Guerra GG, Joffe AR, Mazurak VC, Larsen BM: A Canadian Survey of Perceived Barriers to Initiation and Continuation of Enteral Feeding in PICUs. *Pediatr Crit Care Med* 2013.

38. Meert KL, Daphtary KM, Metheny NA: Gastric vs small-bowel feeding in critically ill children receiving mechanical ventilation: a randomized controlled trial. *Chest* 2004, 126(3):872-878.

39. Hirshberg E, Lacroix J, Sward K, Willson D, Morris AH: Blood glucose control in critically ill adults and children: a survey on stated practice. *Chest* 2008, 133(6):1328-1335.

40. Vlasselaers D: Blood glucose control in the intensive care unit: discrepancy between belief and practice. *Crit Care* 2010, 14(3):145.

41. Boonen E, Van den Berghe G: Endocrine responses to critical illness: novel insights and therapeutic implications. *J Clin Endocrinol Metab* 2014, 99(5):1569-1582.

42. Macrae D, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, Parslow R, Tasker RC, Elbourne D, Investigators CH: A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med* 2014, 370(2):107-118.

Figure legends

Figure 1. Participating countries (in grey).

Figure 2. Caloric intake in different age categories in the point-prevalence; p < 0.001 when comparing intake in the 3 different age categories (Kruskal-Wallis test)

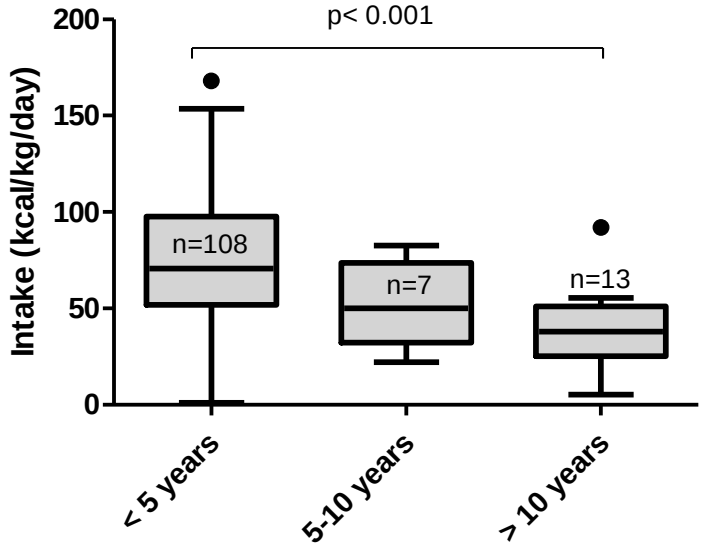


Figure 3. Early initiation of enteral and parenteral nutrition.

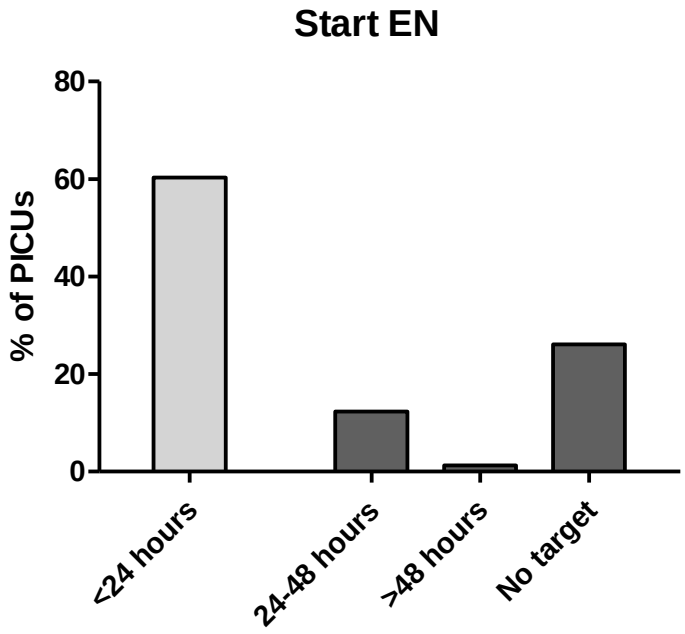
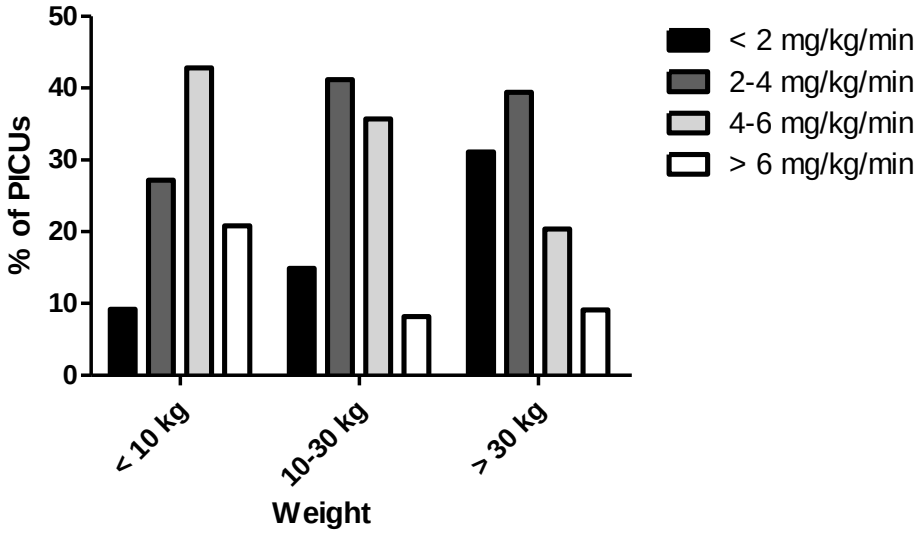


Figure 4. Varying target glucose intake in the first 24 hours of admission.



Tables

Table 1. PICU characteristics of the first (n=156) and point-prevalence part (n=42) of the survey

Characteristic	Number of PICUs (%)	
	Part 1: survey N=156	Part 2: point-prevalence N=42
Continent		
Asia	37 (24%)	9 (21%)
Africa	5 (3.2%)	2 (4.8%)
Europe	48 (31%)	17 (41%)
North-America	33 (21%)	3 (7.1%)
Oceania	9 (5.8%)	2 (4.8%)
South-America	24 (15%)	9 (21%)
Income category (country)		
Low	1 (0.6%)	0 (0.0%)
Lower middle	20 (13%)	2 (4.8%)
Upper middle	49 (31%)	15 (36%)
High	86 (55%)	25 (60%)
Hospital type		
General hospital	31 (20%)	7 (17%)
University hospital	51 (33%)	15 (36%)
Children's hospital	20 (13%)	4 (9.5%)
University-children's hospital	48 (31%)	14 (33%)
Type of PICU		
Multidisciplinary/mixed	135 (86%)	36 (86%)
Cardiac	6 (4.0%)	2 (4.8%)
Medical	8 (5.1%)	2 (4.8%)
Combination of PICU		
With adult ICU	9 (5.8%)	1 (2.4%)
With Neonatal ICU	25 (16%)	8 (19%)
With adult and neonatal	3 (2.0%)	0 (0.0%)
ICU	119 (76%)	33 (79%)
Not combined		
Size of PICU		
1-10 beds	76 (49%)	20 (48%)
11-20 beds	51 (33%)	14 (33%)
21-30 beds	23 (15%)	7 (17%)
>30 beds	6 (3.5%)	1 (2.4%)
Ventilated patients		
< 25%	22 (14%)	5 (12%)
25-50%	55 (35%)	13 (31%)
50-75%	49 (31%)	14 (33%)
>75%	30 (19%)	10 (24%)

Table 2. Characteristics of nutritional protocols

Characteristic	Number of PICUs (%)
	Total 156
Protocol available	82 (52%)
Information in protocol	
Assessment of energy	72 (89%)
requirements	65 (81%)
Protein requirements	57 (71%)
Management of GRV	72 (89%)
Type of EN	75 (94%)
Amount of EN	71 (88%)
Composition of PN	72 (89%)
Amount of PN	
Protocol age/weight differentiated	
Not	6 (7.7%)
For EN	8 (10%)
For PN	7 (8.7%)
For both EN and PN	59 (74%)

GRV: gastric residual volume; EN: enteral nutrition; PN: parenteral nutrition

Table 3. Parenteral lipid emulsions used in the PICU (more than 1 answer possible per PICU)

Lipids by brand	Type	Number of PICUs (%)
Intralipid	100% soy based	101 (65%)
SMOFlipid	30% soy, 25% olive oil, 15% fish oil, 30% MCT	44 (28%)
Omegaven	100% fish oil	16 (10%)
Clinoleic	80% olive oil, 20% soy	27 (18%)
Lipoplus	10% fish oil, 40% soy, 50% MCT	5 (2.9%)
Lipofundin	100% soy based	4 (2.2%)

Table 4.Overview of nutritional recommendations by A.S.P.E.N. and ESPEN/ESPGHAN and clinical practice.

Element	A.S.P.E.N. (2009 (26))	ESPEN/ESPGHAN (2005 (27))	Our survey
Target group	Nutrition in critically ill children	Parenteral nutrition in children Special sections for critically ill children	Nutrition in critically ill children
Nutrition assessment	Screening to identify (risk of) malnutrition	Regular measurements of height, weight and head circumference (<3 years). Skin fold thickness and mid arm circumference reflect body fat and protein. Biochemical measurements are not ideal	Nutritional status administered on admission and during stay, mostly by weight (94%), height (50%) and biochemical measurements (60%).
Nutritional protocols/support	Support team and protocols may enhance delivery of nutrition, no effect on outcome.	A NST should monitor the process of parenteral nutrition	Nutritional support team (56.8%) and protocol (52.4%) available to most PICUs, no effect on caloric intake or % EN.
Energy requirements	EE assessed throughout course of illness. Standard equations often unreliable for estimate of EE. IC desirable in subgroup of patients, if not available, energy provision based on formulas without correction factors.	Reasonable values for EE from prediction equations without stress factors. Measurement of REE may be useful in the individual patient.	Standard equations commonly used; in 70% of PICUs in combination with correction factors, as fever (41%), diagnosis (54%) and growth (59%). IC available in 14% of PICUs.
Timing of nutrition	No recommendations. Current practice is initiation of EN in 48-72 hours.	Time of initiation of PN will depend on individual circumstances and age and size of the child. Inadequate nutrition up to 7 days may be tolerated in older children.	Early initiation of EN and PN. Supplementation of inadequate EN with PN in majority of PICUs. Reaching nutritional targets by EN remains challenging.
Macronutrient intake	Insufficient data at moment of publication to make evidence-based recommendation	Only parenteral recommendations	
Glucose		Glucose intake in critically ill	Varying glucose targets, mostly 2-6 mg/kg/min

		children limited to 5 mg/kg/min	Median glucose intake first 24 hours 1.7 mg/kg/min
Protein	0-2 years: 2-3 g/kg/day 2-13 years: 1.5-2 g/kg/day 13-18 years: 1.5 g/kg/day	Neonates: 1.5-3 g/kg/day 2 months-3 years: 1.5-2 g/kg/day 3-18 years: 1-2 g/kg/day Critically ill children (3-12 years old): 3 g/kg/day amino acids	Varying protein targets, 66% not meeting target
Lipids (iv)	Most centers start at 1 g/kg/day and advance over a period of days to 2-4 g/kg/day with monitoring of TG levels	All children: infants max. 3-4 g/kg/day lipids, older children 2-3 g/kg/day. In PICU: more frequent monitoring and adjustment to TG concentration	Lipid target predominantly 1.5-2.5 g/kg/day, adjusted to TG concentration
Route of nutrition	EN preferred, if tolerated. PN if EN in insufficient. Insufficient data to recommend appropriate site. Gastric route is preferred, post-pyloric may be indicated to improve caloric intake or in children at high risk of aspiration or intolerant to gastric feeds	No recommendations on EN	EN preferred. PN if EN is insufficient. Gastric route is preferred in ventilated (67%) and non-ventilated (88%) patients. Prokinetics are used if a patient is not tolerating feeds.
Immunonutrition	Not recommended based on available literature at moment of publication	Not recommended based on available literature at moment of publication	No data

PICU: pediatric intensive care unit; NST: nutritional support team; EN: enteral nutrition; PN: parenteral nutrition; REE: resting energy expenditure; TG: triglycerides; IC: indirect calorimetry

5. An analysis of reliability and accuracy of muscle thickness ultrasonography in critically ill children and adults

Adapted from:

Fivez T, Hendrickx A, Van Herpe T, Vlasselaers D, Desmet L, Van den Berghe G, Mesotten D. An analysis of reliability and accuracy of muscle thickness ultrasonography in critically ill children and adults. JPEN 2015

Abstract:

Background: Muscle wasting starts already within the first week in critically patients and is strongly related to poor outcome. Nevertheless, the early detection of muscle wasting is difficult. Therefore, we investigated the reliability and accuracy of ultrasonography to evaluate skeletal muscle wasting in critically ill children and adults.

Methods: This prospective observational study enrolled 20 sedated critically ill children and 14 critically ill adults. Two independent investigators made 210 ultrasonographical assessments of muscle thigh thickness. Inter- and intra-observer reliability was calculated and cut-off levels were calculated as a function of muscle thickness and the expected reduction in muscle size (predefined at 20% and 30%).

Results: Average muscle thickness was 1.67 ± SD 0.55 cm in the pediatric and 2.10 ± SD 0.85 cm in the adult population. The median absolute inter-observer variability was 0.07 cm [IQR 0.04 – 0.20 cm] in the pediatric population and 0.05 cm [IQR 0.03 – 0.09 cm] in the adult population. However, the absolute intra-observer accuracy had a 95% confidence interval of 0.43 cm in children and 0.22 cm in adults. Only a 30% decrease (0.50 cm) in muscle thickness can be detected in critically ill children.

Conclusion: Although in the pediatric population the inter-observer variability is acceptable, the intra-observer variability is too large with respect to the expected reduction in muscle thickness. In adults, ultrasonography may be a reliable tool for early detection of muscle mass wasting.

Introduction

Critical illness results in intensive care unit-acquired weakness (ICUAW), especially in patients with a protracted course of disease.(1, 2) ICUAW is associated with prolonged mechanical ventilation, longer ICU and hospital stay and increased mortality. In the longer-term, it also impairs rehabilitation and recovery to fully functional autonomy, leading to poor quality of life.(1, 3, 4)

ICUAW already starts within the first week of critical illness and is associated with this functional disability in the longer term. The ICUAW is the result of a combination of critical illness polyneuropathy and critical illness myopathy. Skeletal muscle wasting is the most typical clinical feature of ICUAW and stems from muscle atrophy. Therapeutic interventions are limited to early mobilization, blood glucose control and limiting the use of glucocorticoids and neuromuscular blocking agents.(5, 6)

Due to the lack of therapeutic options and the important long-term consequences of ICUAW and muscle wasting, their early detection may be essential to steer risk stratification and preventative measures. Assessment of limb muscle strength by functional, volitional measurements, such as the Medical Research Council (MRC)-sum score and handgrip strength, appears to be the gold standard. However, only fully awake and cooperative patients can undergo these measurements, potentially causing a delay in the diagnosis of ICUAW.(7) Therefore, non-volitional muscle strength measurements, such as an electromyogram to detect critical illness polyneuropathy and myopathy, have been used for the early screening for ICUAW. However, this technique is complex, requiring expert's interpretation.(2, 8)

Ultrasound measurements of muscle thickness are also considered to be a non-volitional surrogate for muscle strength.(9) The use of ultrasonography is well integrated in daily ICU-practice. In comparison with computer tomography (CT) and magnetic resonance imaging (MRI), ultrasound measurements of muscle thickness are inexpensive and logistically less cumbersome. When using a strict imaging protocol, the ultrasound measurements correlate well with the CT and MRI measurements.(7, 10, 11) In adult critically ill patients ultrasound measurements of m. quadriceps femoris muscle thickness were

sensitive to detect a decrease in muscle mass in patients with a prolonged ICU-stay.(9) In a recent prospective, ultrasonographical evaluation of muscle wasting in critically ill patients, rectus femoris cross-sectional area was decreased by approximately 18% at day 10.(12) The recent paper of Tilluist et al. highlighted the reliability of bedside ultrasound in assessing muscle thickness in healthy volunteers.(13) However ICUAW is poorly characterized in children, with only case reports as evidence(14, 15). Neither the functional, volitional measurements of muscle strength nor the non-volitional measurements of muscle mass, such as ultrasonography have been validated in the pediatric critically ill patient population. Additionally, ultrasonographical measurements of muscle mass are harder to standardize due to the age-dependency of muscle mass.

In this study we therefore aimed to assess the reliability and accuracy of ultrasound measurements of muscle thickness during critical illness as a function of age, covering the spectrum from neonates to adults. The inter-observer and intra-observer variability were assessed in relation to a predefined decrease in muscle thickness (3).

Methods

Study Design and Population

This prospective observational study in a level III paediatric and adult ICU ran from October 2013 to June 2014 and was part of the PEPaNIC randomized controlled trial (clinicaltrials.gov number: NCT01536275). The study was approved by the ethics committee of the University Hospitals Leuven. Study patients were admitted to the ICU for various reasons such as cardiac surgery, respiratory failure and sepsis. Patients were only included when they were sedated, as a correct position is crucial for optimal scanning. Ultrasonography was performed during the first week of admission, to exclude patients with protracted critical illness. Patients with severe muscle disorders, severe edema, localized inflammation, fractures in the limb femoral lines or were on muscle relaxants were also excluded.

Ultrasonography Protocol

A linear array commercial real time ultrasound scanner (Vivid S6, GE Healthcare, Diegem, Belgium) was used with a 12-MHz transducer. Ultrasonographic images were collected from a transversal scan of the thigh with the patient in supine position, the knee extended and the muscle relaxed. The transducer was placed perpendicular to the long axis of the tight on three fifths of the distance from the anterior superior iliac spine to the superior patellar border. This position was defined beforehand with a surgical skin marker (Devon Surgical Skin Marker, Covidien, Mechelen, Belgium) after measuring the exact position with a tape measure.

An excess of contact gel was applied to minimize image distortion. By obtaining maximal reflection of the bone, optimal transducer orientation was achieved and oblique scanning was minimized. A staff member of the department of radiology extensively trained the two independent researchers (TF, AH) to perform these measurements correctly and individually. All images were analyzed directly on the ultrasound scanner (Figure 1). Muscle thickness was defined as the distance between the superior

border of the muscle and the cortex of the femur. Each limb of the patient was measured two times by the two investigators, independently of each other.

Statistical Analysis

The coefficient of variation was calculated for duplicate measurements. In the linear regression analysis (Pearson correlation coefficient), results are represented with R^2. In the Bland-Altman test the 95% limit of agreement, defined as ± 1.96 Standard Deviation (SD) of the means of the non-absolute differences between the paired measurements by the two observers were represented. Further the absolute differences, i.e. independent of the sign of the difference (both positive and negative values), was computed. Reliability was assessed by the intraclass correlation coefficient (ICC), using a model for 2-way random single measures (consistency). Reliability is higher when the ICC is closer to 1.0. A p-value of less than 0.05 was deemed statistically significant. For the statistical analyses Matlab (R2012a The MathWorks Inc, Natick, MA, USA) was used.

Results

Pediatric group

A group of 30 patients were included in the study. The patients' demographics are shown in table 1. In one child the measurement could not be done because of a central venous line in the femoral vein. The coefficient of variation of duplicate measurements (n=105) was 4.51% for operator 1 and 5.1% for operator 2. The coefficient of determination (R^2) was 0.94 ($p<0.0001$). The average muscle thickness was 1.67 cm (SD: 0.55 cm) as shown in table 2. The absolute intra-observer variability, as expressed by the limits of agreement (± 1.96 SD, containing 95% of the samples for normally distributed samples), was 0.42 cm for operator 1 and 0.45 cm for operator 2. Both distributions of the non-absolute differences are visualized in a Bland-Altman plot in Figure 2. The median absolute inter-observer variability was 0.07 cm [IQR 0.032 – 0.19 cm]. The intraclass correlation coefficient between the two observers covering measurements was 0.98 for single measures.

Adult Group

A group of 14 patients were included in the study. The patients demographics are shown in table 1. The coefficient of variation of duplicate measurements (n=86) was 1.91% for operator 1 and 1.32% operator 2. The coefficient of determination (R^2) was 0.99 ($p<0.0001$). The average muscle thickness was 2.10 cm (SD: 0.85 cm) as shown in table 3. The absolute intra-observer variability, as expressed by the limits of agreement (± 1.96 SD, containing 95% of the samples for normally distributed samples), was 0.33cm for operator 1 and 0.12 cm for operator 2. Both distributions of the non-absolute differences are visualized in a Bland-Altman plot in Figure 3. The median absolute inter-observer variability was 0.05 cm [IQR 0.03 – 0.09 cm]. The intraclass correlation coefficient between the two observers covering 86 measurements was 0.99 for single measures.

The intra-observer 95% CI of ultrasound measurement of muscle thickness is greater than the predefined 20 % decrease in the average muscle thickness in our pediatric ICU population.(3) In adult critically ill patients the intra-observer 95% CI of the ultrasound measurements (0.22 cm) is well below the predefined decrease in muscle thickness. The accuracy in relation to the predefined decrease in muscle thickness is shown in table 5. The 95 % CI Bland- Altman is the average of both absolute intra observer variability as the sign of the differences is not clinical relevant.

Discussion

Ultrasonographical measurement of muscle thickness in critically ill children can easily be done in sedated critically ill children and adults with low inter-observer variability. However, the moderate accuracy and high intra-observer variability do not allow reliably detecting a decrease in muscle thickness in the pediatric ICU population.

In adult critically ill patients, the measurement of the thickness of the M. quadriceps femoris with ultrasound may be a good indicator of muscle wasting (16). Dubowitz and Heckmatt showed that ultrasonography may be useful in children in the diagnosis of neuromuscular diseases (17, 18). Little data is available about ICUAW and muscle wasting in pediatric critical illness. The incidence may be lower as their risk factors, multiple organ failure and protracted critical illness, are less common (3). Parenteral nutrition, supplementing insufficient enteral nutrition, as often administered to prevent muscle wasting in critically ill children. However in adult critical ill patients it has been recognized that aggressive nutritional therapy does not prevent loss of lean body mass and leads to increase of adipose tissue (19, 20). In critically ill children no large clinical trials have looked at the impact of PN on patient centre outcome (21). One study suggest that even 6 months after a burn injury muscle protein deposition cannot be improved by amino acid infusions (22).

Alongside the PEPaNIC randomized controlled trial, in which early versus late initiation of parenteral nutrition is compared in critically ill children, this study assessed the accuracy and reliability of ultrasound measurements of muscle thickness to detect muscle wasting. Similar measurements were done in critically ill adults, as more data are available in this population.

In our pediatric population the inter-observer variability is acceptable and comparable to the measurements in the adult population. However, the intra-observer variability was much larger in the pediatric than in the adult population. When taking into account the predefined decreases of muscle thickness, ultrasound measurements of muscle thickness may only be just accurate and reliable enough in the adult population.

This may explain why rectus femoris muscle thickness, assessed by ultrasound, did not decrease over time (1, 23). There are ample reasons to explain this high intra operator variability: slight changes in angle, alteration in application of pressure and the presence of edema in critically ill patient. These pitfalls for inappropriate accuracy can only be compensated by rigorous training of the examiners and strict standardization of the ultrasound settings and protocol.

Our measurements correlate with the results in the recent paper of Tillquist et al and highlight the accuracy of and reliability of ultrasonography in muscle thickness assessment by different observers.(13) The differences in reliability between the operators in this paper and the latter might be correlated with the study population. The majority of the study patients in this study were in ICU for a longer time upon muscle thickness assessment. Certainly, more studies, that cover a wide range of critically ill patients regarding their severity of disease but also their baseline muscle mass, need to be done to confirm the potential of ultrasound measurement of muscle thickness in critically ill adults.

Instead of muscle thickness as a marker, ultrasound assessment of muscle echogenicity and the measurement of the cross-sectional area of the muscle may be promising alternatives (3,8). However all these surrogate markers of ICUAW need to be validated against patient centered functional outcomes. Quantification of muscle mass by CT-scan, with an inter-observer CV of 0% and an ICC of 0.998, appears to be much more reliable than ultrasound measurements (20). However, the risks associated with CT-scanning currently do not outweigh the benefit of an early detection of a rather limited (10-30%) loss in muscle mass without the prospect of treatments for muscle wasting. These risks of CT scanning encompass patient instability during transportation but also secondary malignancies in the long run(24).

This study has several limitations though. First, no serial assessments of muscle thickness were done to evaluate the decrease in muscle thickness over time. Instead we tested the ultrasound measurements against predefined values, based on the literature, as it is impossible to predict the length of stay in the ICU. Second, the ultrasound measurements of muscle thickness were neither compared with muscle cross-sectional area or echogenicity, nor with functional markers, such as handgrip strength or MRC-

SUM. Third, we mainly included newborns and young children, since this represents the vast majority of critically ill children in tertiary referral pediatric ICUs. As muscle mass increases with the bodyweight (25), it can be hypothesized that from a certain body weight onwards the intra-observer variability may become acceptable.

In conclusion, ultrasonographical assessment of muscle thickness is hampered by high intra-observer variability. It may be used in critically ill adults to evaluate muscle wasting. However, its low accuracy and reliability, in light of the small drop in muscle thickness to be detected, make it unsuitable for the pediatric ICU population. Further standardization of the ultrasound protocols may improve its performance.

Table 1. Baseline Demographics

	Pediatric Group (n=30)	**Adult Group (n=14)**
Biometrics		
Age – yr (IQR)	3 (1.3 - 6)	73 (63 - 77)
Weight – kg (IQR)	12.2 (5.8 – 19.8)	71 (67 - 82)
Height – cm ± SD	92.4 ± 35.6	173.5 ± 6.5
Severity of illness		
Score ± SD	11 ± 5 (PRISM)	21 ± 8 (APACHE-II)
Intubated – n (%)	22 (73%)	14 (100%)
Ventilated – n (%)	29 (97%)	14 (100%)
Vasopressors – n (%)	3 (10%)	13 (93%)
Inotropics – n (%)	8 (27%)	3 (21%)
Diagnostic category		
Medical – n (%)	18 (60%)	2 (14%)
Cardia Surgery – n (%)	7 (23%)	7 (50%)
Other Surgery – n (%)	2 (2%)	1 (7%)
Neurlogical – n (%)	2 (2%)	3 (21%)
Transplantation – n (%)	1 (1%)	1 (7%)

Table 2. Results of ultrasound measurements in Pediatric patients

Parameter	Average muscle thickness	Intra-variability operator 1	Intra-variability operator 2	Inter-variability between 2 operators
MEAN	**1,67**	0,11	0,11	0,11
SD	**0,55**	0,11	0,11	0,10
MEDIAN	**1,61**	0,07	0,06	0,07
Q25	**1,3**	0,03	0,03	0,03
Q75	**1,88**	0,17	0,18	0,19
Bland-Altman				
2*1.96*SD		0,41	0,45	0,39

Table 3. Results of ultrasound measurements in adult patients

Parameter	Average muscle thickness	Intra-variability operator 1	Intra-variability operator 2	Inter-variability between 2 operators
MEAN	**2,10**	0,05	0,03	0,08
SD	**0,85**	0,08	0,03	0,09
MEDIAN	**1,79**	0,03	0,03	0,05
Q25	**1,44**	0,02	0,01	0,03
Q75	**2,94**	0,06	0,05	0,09
Bland-Altman				
2*1.96*SD		0,33	0,12	0,34

Table 4: Accuracy in relation to predefined decreases in muscle thickness

Subgroup	20% decrease	30% decrease	95% CI Bland-Altman
Paediatric	0.34 cm	0.50 cm	0.39 cm
Adult	0.42 cm	0.63 cm	0.22 cm

Figure 1. Screenshot of a muscle thickness measurement by ultrasound. Transversal scan of the thigh with the patient in the supine position, with the knee extended and the muscle relaxed. Muscle thickness is measured by the distance between the superior border of the muscle and the cortex of the femur.

Figure 2. Bland-Altman plot of the muscle thickness measurements in pediatric critically ill patients. Operator 1 (circles); operator 2 (stars).

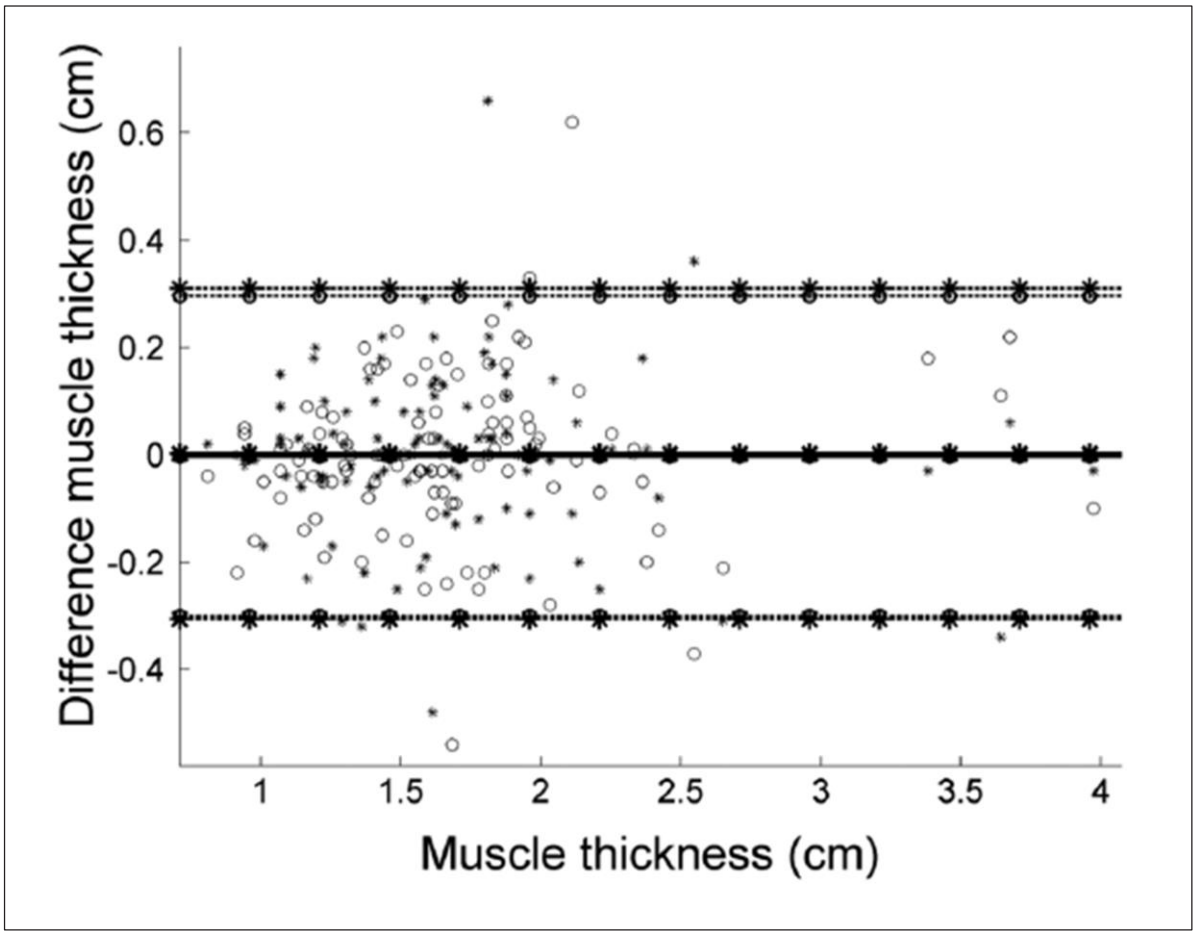
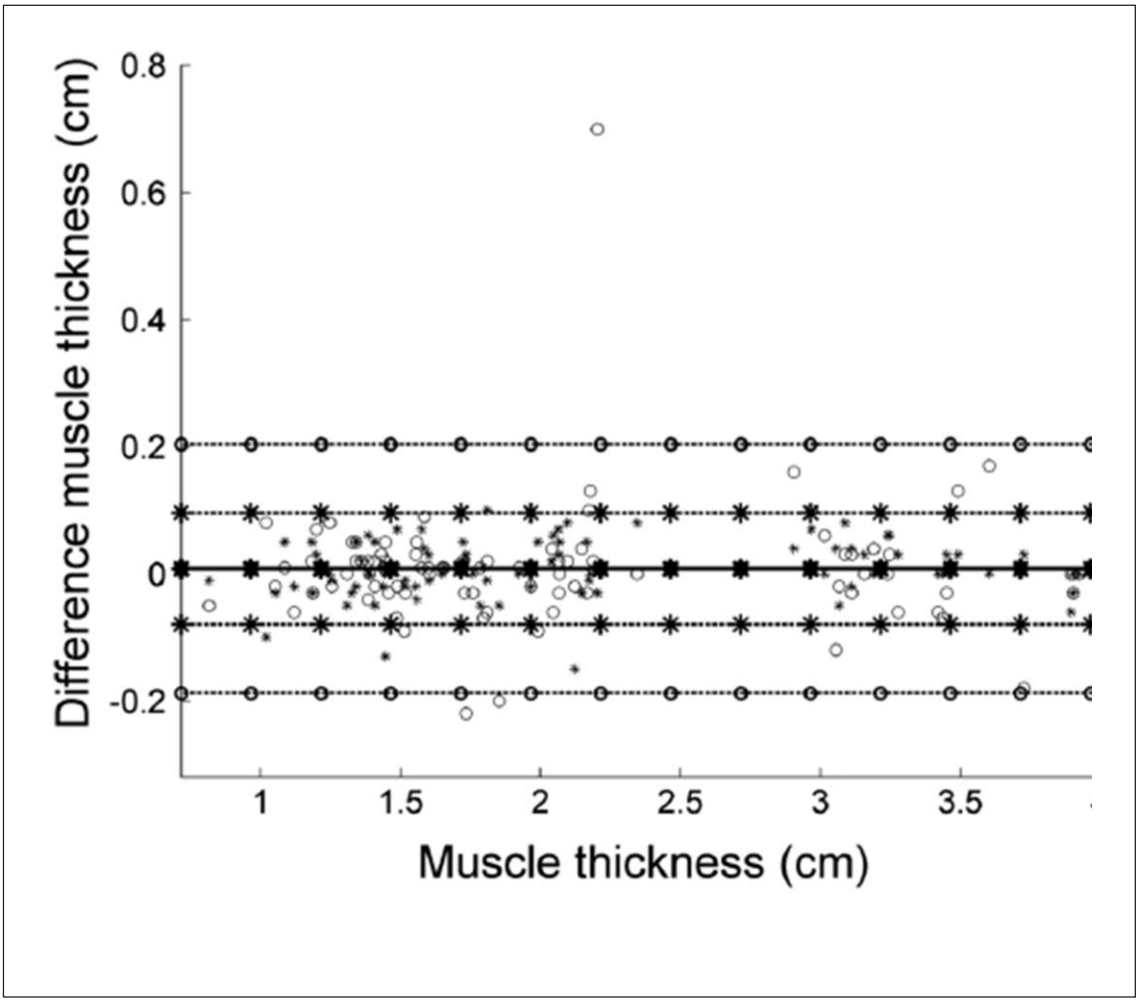


Figure 3. Bland-Altman plot of the muscle thickness measurements in adult critically ill patients. Operator 1 (circles); operator 2 (stars).



References

1. Herridge MS, Tansey CM, Matte A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. The New England journal of medicine. 2011 Apr 7;364(14):1293-304. PubMed PMID: 21470008.

2. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. The New England journal of medicine. 2014 Apr 24;370(17):1626-35. PubMed PMID: 24758618. Epub 2014/04/25. eng.

3. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA : the journal of the American Medical Association. 2013 Oct 16;310(15):1591-600. PubMed PMID: 24108501.

4. Schweickert WD, Hall J. ICU-acquired weakness. Chest. 2007 May;131(5):1541-9. PubMed PMID: 17494803.

5. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. The Lancet Respiratory medicine. 2013 Oct;1(8):621-9. PubMed PMID: 24461665.

6. Hermans G, Wilmer A, Meersseman W, Milants I, Wouters PJ, Bobbaers H, et al. Impact of intensive insulin therapy on neuromuscular complications and ventilator dependency in the medical intensive care unit. American journal of respiratory and critical care medicine. 2007 Mar 1;175(5):480-9. PubMed PMID: 17138955.

7. Hermans G, Van Mechelen H, Clerckx B, Vanhullebusch T, Mesotten D, Wilmer A, et al. Acute Outcomes and 1-Year Mortality of Intensive Care Unit-acquired Weakness. A Cohort Study and Propensity-matched Analysis. American journal of respiratory and critical care medicine. 2014 Aug 15;190(4):410-20. PubMed PMID: 24825371.

8. Lacomis D. Electrophysiology of neuromuscular disorders in critical illness. Muscle & nerve. 2013 Mar;47(3):452-63. PubMed PMID: 23386582.

9. Puthucheary Z, Montgomery H, Moxham J, Harridge S, Hart N. Structure to function: muscle failure in critically ill patients. The Journal of physiology. 2010 Dec 1;588(Pt 23):4641-8. PubMed PMID: 20961998. Pubmed Central PMCID: 3010132.

10. Dupont AC, Sauerbrei EE, Fenton PV, Shragge PC, Loeb GE, Richmond FJ. Real-time sonography to estimate muscle thickness: comparison with MRI and CT. Journal of clinical ultrasound : JCU. 2001 May;29(4):230-6. PubMed PMID: 11323778.

11. Arbeille P, Kerbeci P, Capri A, Dannaud C, Trappe SW, Trappe TA. Quantification of muscle volume by echography: comparison with MRI data on subjects in long-term bed rest. Ultrasound in medicine & biology. 2009 Jul;35(7):1092-7. PubMed PMID: 19394755.

12. Grimm A, Teschner U, Porzelius C, Ludewig K, Zielske J, Witte OW, et al. Muscle ultrasound for early assessment of critical illness neuromyopathy in severe sepsis. Critical care. 2013;17(5):R227. PubMed PMID: 24499688. Pubmed Central PMCID: 4057413.

13. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, Kummerlen C, Leung R, Stollery D, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. JPEN Journal of parenteral and enteral nutrition. 2014 Sep;38(7):886-90. PubMed PMID: 23980134.

14. Kukreti V, Shamim M, Khilnani P. Intensive care unit acquired weakness in children: Critical illness polyneuropathy and myopathy. Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2014 Feb;18(2):95-101. PubMed PMID: 24678152. Pubmed Central PMCID: 3943134.

15. Williams S, Horrocks IA, Ouvrier RA, Gillis J, Ryan MM. Critical illness polyneuropathy and myopathy in pediatric intensive care: A review. Pediatr Crit Care Med. 2007 Jan;8(1):18-22. PubMed PMID: 17251877.

16. Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. The American journal of clinical nutrition. 1995 Sep;62(3):533-9. PubMed PMID: 7661114.

17. Heckmatt JZ, Pier N, Dubowitz V. Measurement of quadriceps muscle thickness and subcutaneous tissue thickness in normal children by real-time ultrasound imaging. Journal of clinical ultrasound : JCU. 1988 Mar-Apr;16(3):171-6. PubMed PMID: 3150398.

18. Heckmatt JZ, Pier N, Dubowitz V. Real-time ultrasound imaging of muscles. Muscle & nerve. 1988 Jan;11(1):56-65. PubMed PMID: 3277050.

19. Hart DW, Wolf SE, Herndon DN, Chinkes DL, Lal SO, Obeng MK, et al. Energy expenditure and caloric balance after burn: increased feeding leads to fat rather than lean mass accretion. Annals of surgery. 2002 Jan;235(1):152-61. PubMed PMID: 11753055. Pubmed Central PMCID: 1422407.

20. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Guiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Critical care medicine. 2013 Oct;41(10):2298-309. PubMed PMID: 23860247.

21. Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, et al. Nutritional support for critically ill children. Cochrane Database Syst Rev. 2009 (2):CD005144. PubMed PMID: 19370617. Epub 2009/04/17. eng.

22. Tuvdendorj D, Chinkes DL, Zhang XJ, Sheffield-Moore M, Herndon DN. Skeletal muscle is anabolically unresponsive to an amino acid infusion in pediatric burn patients 6 months postinjury. Annals of surgery. 2011 Mar;253(3):592-7. PubMed PMID: 21263308. Pubmed Central PMCID: 3632299.

23. Cartwright MS, Kwayisi G, Griffin LP, Sarwal A, Walker FO, Harris JM, et al. Quantitative neuromuscular ultrasound in the intensive care unit. Muscle & nerve. 2013 Feb;47(2):255-9. PubMed PMID: 23041986.

24. Wen JC, Sai V, Straatsma BR, McCannel TA. Radiation-related cancer risk associated with surveillance imaging for metastasis from choroidal melanoma. JAMA ophthalmology. 2013 Jan;131(1):56-61. PubMed PMID: 23307209.

25. Scholten RR, Pillen S, Verrips A, Zwarts MJ. Quantitative ultrasonography of skeletal muscles in children: normal values. Muscle & nerve. 2003 Jun;27(6):693-8. PubMed PMID: 12766980.

6. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial

Adapted from:

Fivez T. Kerklaan D*, Verbruggen S, Vanhoebeek I, Verstraete S, Tibboel D, Guerra GC, Wouters PJ, Joffe A, Joosten K, Mesotten D, Van den Berghe G.Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. Trials 2015; 16: 202*

** Equal contribution*

ABSTRACT

Background

The state-of-the-art nutrition used for critically ill children is based essentially on expert opinion and extrapolations from adult studies or on studies in non-critically ill children. In critically ill adults, withholding parenteral nutrition (PN) during the first week in ICU improved outcome, as compared with early supplementation of insufficient enteral nutrition (EN) with PN. We hypothesized that withholding PN in children early during critical illness reduces the incidence of new infections and accelerates recovery.

Methods/design

The Pediatric Early versus Late Parenteral Nutrition in Intensive Care Unit (PEPaNIC) study is an investigator-initiated, international, multicenter, randomized controlled trial (RCT) in three tertiary referral pediatric intensive care units (PICUs) in 3 countries on 2 continents. This study compares early versus late initiation of PN when EN fails to reach preset caloric targets in critically ill children. In the early-PN (control, standard of care) group, PN comprising glucose, lipids and amino acids is administered within the first days to reach the caloric target. In the late-PN (intervention) group, PN completing EN is only initiated beyond PICU-day 7, when EN fails. For both study groups, an early EN protocol is applied and micronutrients are administered intravenously. The primary assessor-blinded outcome measures are the incidence of new infections during PICU-stay and the duration of intensive care dependency. The sample size (n=1440, 720 per arm) was determined in order to detect a 5% absolute reduction in PICU infections, with at least 80% one-tailed power (70% two tailed) and an alpha error rate of 5%. Based on the actual incidence of new PICU infections in the control group, the required sample size was confirmed at the time of an *a priori* planned interim-analysis focusing on the incidence of new infections in the control group only.

Discussion

Clinical evidence in favor of early administration of PN in critically ill children is currently lacking, despite potential benefit but also known side effects. This large international RCT will help physicians to gain more insight in the clinical effects of omitting PN during the first week of critical illness in children.

Trial registration

ClinicalTrials.gov: NCT 01536275 on 16 February 2012.

Keywords: Critical illness, children, nutrition, sepsis, lipid, protein, glucose, infection

Background

Nutritional support for children in intensive care

The state-of-the-art nutrition used for critically ill children is essentially based on expert opinion, small studies with surrogate endpoints and extrapolations from adult studies or from studies in healthy children outside the ICU. It is widely accepted that in healthy children, nutrition not only serves to maintain body tissues but also allows growth which is considered of particular importance during infancy and adolescence [1, 2]. In hospitalized children, especially in the young, the current European and American guidelines for nutrition recommend early parenteral nutrition (PN) to prevent/correct malnutrition and to sustain appropriate growth when enteral nutrient (EN) supply is insufficient [3, 4]. Observational studies suggest that about a quarter of children, most notably infants, admitted to pediatric intensive care units (PICUs) develop a pronounced caloric deficit [1]. The stores of energy, fat and protein in children are limited, leaving children to rely on muscle mass to provide necessary substrates for metabolism. The energy deficit observed with acute critical illness in children has been associated with adverse outcome [5]. Based hereon, it is current practice in PICUs to start PN in the acute phase of critical illness to supplement insufficient EN with the intention to avoid underfeeding [3, 4]. However, overfeeding may also be harmful [6-9]. It is difficult to administer the correct amount of nutrition avoiding overfeeding as well as underfeeding.

Varying nutritional guidelines and clinical practices

It is currently advised to assess energy expenditure considered to reflect energy requirements, through the use of indirect calorimetry during the course of critical illness and to use this technique for determining individualized targets to guide nutritional therapy [10]. However, a European survey conducted in 2004 showed that only 17% of the PICUs use this technique [11] and the technique itself has not been well standardized [12, 13]. In the most critically ill, major caveats are present such as respiratory support with more than 40% oxygen and the use of uncuffed tubes resulting in unpredictable

measures. The use of standard equations to predict energy expenditure and/or requirements also carries the risk of overfeeding and underfeeding [14-16].

Experts worldwide agree that there are insufficient data to make evidence-based recommendations for the optimal target of caloric intake in critically ill children and for the optimal time after onset of critical illness by which this target should be reached. The lack of widely accepted caloric targets for critically ill children results in nutritional strategies that vary substantially across centers. The current European and American guidelines for nutrition in hospitalized children recommend PN to prevent or correct malnutrition and to sustain appropriate growth when EN supply is insufficient [10, 17]. Most guidelines advise to do this early so that the recommended daily allowances for children are reached on day 2 or 3 after PICU admission. These recommendations are based on evidence from cohort studies without a control group, case series or expert opinion (Grade D level).

The ongoing controversy on optimal amount, composition and timing of administration of PN in critically ill children may in fact conceal the fact that there is no hard evidence for any use of PN in critically ill children. Supported by the results of a Cochrane systematic review, Joffe et al. concluded that randomized trials investigating the role of intravenous nutritional support during the first week of critical illness in children should be performed and should include a control arm in which no nutritional support is administered or hypocaloric goals (below basal metabolic rate) for nutritional support are used [18].

Rationale of the study and study hypothesis

A recent RCT in critically ill adults [19] showed that the early provision of PN worsened rather than improved outcomes as compared with withholding PN and thus tolerating a substantial caloric deficit up to one week in ICU. Also other studies did not show clinical benefit of early PN in adult ICU patients [20, 21]. Hitherto, no well-designed RCT has been performed in critically ill children. The aim of the PEPaNIC trial (the acronym stands for **P**ediatric version of the effect of **E**arly **Pa**renteral **N**utrition to complete insufficient enteral nutrition in **IC**U patients) is to investigate whether a strategy of withholding

PN during the first 7 days in the PICU (late PN) provides clinical benefit over the current practice of early PN in critically ill children. We hypothesize that withholding PN for one week in the PICU reduces new infections and shortens the duration of PICU-stay.

This hypothesis is currently being tested in a multicenter superiority RCT performed in three large, tertiary referral PICUs (University Hospitals Leuven, Leuven, BE – Erasmus MC - Sophia Children's Hospital, Rotterdam, NL – Stollery Children's Hospital, Edmonton, CA). The centers were invited to participate based on a self-declared routine use of early PN in the PICU. It was anticipated that this routine use of early PN differs among centers. This was considered to be an asset as it contributes to the external validity of the PEPaNIC trial.

Methods/design

Ethical approval

The study protocol and (deferred) informed consent forms were approved by the institutional ethical review boards in Leuven BE (ML8052 Amend-ID0005), Rotterdam NL (NL38772.000.12) and Edmonton CA (Pro00038098). Informed consent is given in writing by the parents or the legal guardians, confirmed by the child when older than 7 years, after providing all information orally in plain language and in writing. For planned admissions, informed consent is obtained prior to surgery/procedure. For unplanned admissions, informed consent is obtained within 24 hours after admission on the PICU (deferred informed consent as the nutritional therapy should be initiated from PICU admission onward).

Patients' eligibility – Inclusion criteria

Upon admission to the participating PICUs, all critically ill children are screened for nutritional risk and eligibility for inclusion in the PEPaNIC clinical study [22]. All non-eligible patients, identified by the local investigators, are logged.

Critically ill children, newborn to 17 years (inclusive or exclusive depending on the local definition of a pediatric patient) old, with a STRONGkids (Nutritional risk score) score of 2 points or more and who are likely to stay in the PICU for more than 24h, are eligible for inclusion [22].

Exclusion criteria

Patients fulfilling one or more of the following criteria are excluded:

- STRONGkids score lower than 2 on PICU admission [22]
- Not critically ill (e.g. anticipated oral intake within 24 hours)
- Non-pediatric patients (Age 17 or older cfr. above)
- Premature newborns (<37 weeks gestational age upon admission in the PICU)
- "Do not resuscitate" code at the time of PICU admission

- Expected death within 12 hours
- Readmission to PICU after already having been randomized
- Enrollment in another intervention trial
- Transfer from another PICU or neonatal ICU after a stay of more than 7 days
- Ketoacidotic or hyperosmolar coma
- Inborn metabolic diseases requiring specific diet
- Short bowel syndrome or other conditions requiring PN for more than 7 days prior to PICU admission

Data collection at study entry

At baseline, data on demographic (age, gender, race/ethnicity, (pre-)admission bodyweight and height) and clinical characteristics of the patients are obtained. For all patients severity of illness scores are calculated such as the Pediatric Logistic Organ Dysfunction PELOD score and, for cardiac surgery patients, the Risk-Adjustment in Congenital Heart Surgery or RACHS score. The Pediatric RISk of Mortality (PRISM) score cannot be used for this study as the nutritional management is expected to affect the highest blood glucose concentration during the first 24 hours. In addition, co-morbidities prior to admission are noted. These comprise, among others, the presence of a genetic syndrome, gestational age at birth, presence/history of cancer, diabetes mellitus, kidney failure and infection upon admission.

Randomized treatment allocation

Randomization procedure

Randomization to early PN or late PN in a one to one ratio, is performed centrally (KU Leuven, Belgium) by use of a dedicated computerized system, accessible in all centers 24-hours around the clock, 7 days a week. The computer algorithm allocates every consecutive, eligible patient per center to one of the

two treatment arms in a blinded fashion by use of permuted blocks per diagnostic stratum to create parallel groups. The block size is unknown to bedside physicians, nurses and members of the research team. Patients are stratified per study site according to age groups (<1 year and ≥ 1 year) and the following primary diagnostic categories on admission:

I Medical-PICU admissions (infectious or non-infectious): (a) neurological (b) other.

II Surgical-PICU admissions (elective or emergency) according to referral discipline (a) cardiac surgery (b) other.

Treatment allocation and blinding

Concealed allocation to the randomized treatment was realized by use of the computerized randomization system described above. It was considered not feasible to blind treating physicians and patients for the allocated treatment during the time window of the randomized intervention. After discharge to the normal ward, all treating physicians are unaware of the randomized treatment allocation. All outcome assessors and investigators not directly involved in the patients care, such as statisticians, infectious disease specialists and laboratory personnel, are fully blinded to treatment allocation.

Common strategy for early EN in both study arms

The initiation and increase of EN, and the use of gastroprokinetics are prescribed in the standing orders for EN in each center. Both groups receive micronutrients (trace elements, minerals and vitamins) intravenously from day 2 onwards until the amount of EN given reaches 80% of the caloric target.

Randomized interventions

Patients randomized to the early PN strategy (standard of care or control group) receive this type of nutrition according to current management in each of the participating centers, which were recruited

based on a routine use of early PN. For patients randomized to the late PN group (intervention group), all PN is withheld during the first week in the PICU. The international setting of the trial brings some variation in the control group (see study rationale and hypothesis), while the intervention group is strictly standardized ("no PN during the first week in PICU").

Standard of care or control group: early-PN

In the Leuven (BE) PICU, patients randomized to the early-PN group receive a mixture of glucose 30% and Vaminolact® (Fresenius, Sweden) in equal amounts upon admission to PICU, comprising 150 mg/ml glucose and 4.7 mg/ml nitrogen. For patients who require fluid restriction, total fluid intake is 50 ml/m²/h on day 1 and 2 (the day after admission and further referred to as day 2), and 60 ml/m²/h on day 3. Patients not requiring fluid restriction receive 100 ml/kg/day for the first 10 kg bodyweight, 50 ml/kg for the next 10 kg, and 20 ml/kg for the bodyweight over 20 kg, to be reached within 3 days. For all patients on intravenous (IV) nutrition, and within the fluid limitation described above, lipids [SMOFlipid® (20g/100ml) Fresenius, Sweden] are added from the second morning after admission, initially at a dose of 1.5 g/kg/day, increasing to a maximum of 3 g/kg/day, depending on the age. On the third morning after admission, pharmacy-prepared PN preparations are prescribed, unless adequate enteral nutritional intake is expected. PN preparations contain a mixture of glucose 50% and SMOFlipid® covering respectively 60-70% and 40-30% of calculated energy target and a 1.5-2.5 g/kg protein intake, according to age, by Vaminolact®. If the body weight is above 5 kg, Vaminolact® is replaced by Vamin 18®. Any enterally delivered energy is taken into account twice daily to reduce the energy delivered by PN. When EN covers 80% of optimal calculated caloric needs, PN is stopped. When the patient starts to take oral nutrition, the PN and/or EN is reduced and eventually stopped. Whenever enteral or oral intake falls below 50% of calculated caloric needs, the PN is restarted.

In the Rotterdam (NL) PICU, patients randomized to the "early PN" group receive a continuous glucose infusion upon admission to PICU (< 30 kg; 4-6 mg/kg/min, > 30 kg; 2-4 mg/kg/min). From day 2 onwards

the glucose intake is increased for all children on IV nutrition to 8.3 mg/kg/min (5-10 kg), 6.9 mg/kg/min (10-30 kg) or 4 mg/kg/min (> 30 kg). Primene® (Baxter) (5.5 – 5.7 mg/ml nitrogen) is added from day 2 onward at 25 ml/kg/day (<10 kg) or 20 ml/kg/day (10-30 kg). From day 2 onwards, Intralipid® (Baxter) is added initially at a dose of 10 ml/kg/day (<10 kg) or 7.5 ml/kg/day (10-30 kg), increasing to 20 or 15 ml/kg/day respectively. For patients who require fluid restriction, intake is adjusted accordingly. Children >30 kg on IV nutrition receive from day 2 onwards Olimel N5 (Baxter, 5.2 mg/ml nitrogen, 115 mg/ml glucose) when central lines are in place or Olimel N4 (Baxter, 4.0 mg/ml nitrogen, 75 mg/ml glucose) when only peripheral lines are in place. The dose is 48 ml/kg/day. Any enterally delivered energy is assessed twice daily and the energy delivered by PN is reduced accordingly. Energy goals for enteral nutrition are based on the body weight-based Schofield equation [23] (first day of admission) and on the Recommended Dietary Allowances (RDA, Dutch Health Council) for the subsequent length of stay (Dietary Reference Intake: energy, protein and digestible carbohydrates, 2001, Health Council of the Netherlands: The Hague). Energy goals and composition of parenteral nutrition are based on the ESPGHAN guidelines [4]. When EN covers 80% of calculated caloric needs, PN is stopped. When the patient starts with oral nutrition, PN and/or EN is reduced and eventually stopped. Whenever enteral or oral intake falls below 50% of calculated caloric needs, PN is restarted.

In the Edmonton (CA) PICU, the patient's energy expenditure is assessed upon admission by a registered dietitian when possible. Nutritional support is initiated as soon as possible, with the goal to match energy expenditure (measured or estimated resting energy expenditure of the child). The urgency of initiation of nutrition support is dependent on nutritional risk prior to admission, disease state and age. If indirect calorimetry cannot be done, 65% of basal metabolic rate is used (FAO-WHO) to determine caloric requirement. This number is adjusted daily by the dietitian based on the acute phase response and clinical picture of the child. If nutritional requirements cannot be met enterally, PN is added to achieve caloric target. On admission to PICU, patients receive a glucose infusion of approximately 3-4

mg/kg/minute taking into account the total fluid prescribed by medical staff. At that time EN is initiated when possible. On the morning of day 2, if the patient is not already on full enteral feeding, 20% IV lipids are initiated at 0.5 g/kg/day. On the morning of day 3, if the patient is not already on full enteral feeding, lipid infusion is increased to 1 g/kg/day and a solution of amino acids and concentrated glucose is added. The caloric goal is Basal Metabolic Rate when the patient is intubated and Total Energy Expenditure when the patient has been extubated.

Intervention group: late-PN

In the three centers, patients randomized to the late-PN group receive a mixture of Glucose 5% and NaCl 0.9% at, respectively, 60% and 40% of the total flow rate that is required to obtain optimal hydration, as prescribed by the attending physician, taking into account the volume of EN that is being delivered. No other forms of PN (lipid or protein infusions) are administered. When the amount of EN that is administered still covers less than 80% of the calculated targets after 1 week in the PICU, supplemental PN is initiated on day 8 according to the current PN protocols in each center.

The medical and nursing staff of the PICU were all informed and trained extensively during regular meetings before the start of the trial and were familiarized with the protocol. In order to optimize protocol compliance, the protocol was programmed in the patient data management system (PDMS). The use of this program was explained to every nurse, trainee and resident on the PICU and was always supervised by the senior staff.

Adherence to the protocol in Leuven and Rotterdam was guaranteed by using a PDMS guided system and by careful follow-up by study nurses. In Edmonton, a paper protocol was used and adherence checked by an independent study nurse and physician.

Criteria for stopping the study intervention

When in the intervention arm (late PN group), blood glucose concentration falls spontaneously (without exogenous insulin) below 50 mg/dl, the standard infusion of glucose 5% is switched to 10% glucose until blood glucose concentration is higher than 80 mg/dl and stable. Thereafter, the infusion of glucose 10% is stopped again and switched back to glucose 5%.

Blood glucose management

In Leuven, patients in both study groups receive continuous insulin infusion to target blood glucose levels of 50-80 mg/dl when aged <1y and 70-100 mg/dl when aged ≥ 1 year. Blood glucose and potassium are monitored systematically every 1 to 4 hours on the blood gas analyzer (ABL Radiometer, Copenhagen, Denmark) using undiluted arterial blood samples drawn via a VAMP® system [24] and insulin infusion is adjusted when needed.

In Rotterdam, patients in all age groups receive continuous insulin infusion using a step-wise nurse-driven glucose control protocol to target blood glucose levels of 72-145 mg/dl, except for patients with traumatic brain injury for whom the target is set at 108-145 mg/dl [25]. Blood glucose and potassium are monitored systematically every 1 to 3 hours on the blood gas analyzer (ABL 625; Radiometer, Copenhagen, Denmark) using arterial or capillary blood samples.

In Edmonton, patients in all age groups receive continuous insulin infusion at the discretion of the attending physician when blood glucose levels exceed 180 mg/dl. The attending physician sets the lower target range limit.

Other procedures and guidelines

Other medical treatments are not described by the study protocol. Patients are weaned from the ventilator and from hemodynamic support according to standardized guidelines used in each participating PICU. End-of-life decisions when further intensive care is considered to be futile are taken in consensus by senior PICU physicians and the referring specialist.

Handling of re-admissions to the PICU

Patients who are readmitted to the PICU after a participation in PEPaNIC are not eligible for reinclusion. Patients who are readmitted to the PICU within 48 hours of discharge and who are still within the 7 days' time window of the initial randomization receive the nutrition strategy they were randomly assigned to during the initial PICU admission. Patients readmitted more than 48 hours after PICU discharge will be fed at the discretion of the attending physician (standard care).

Outcome Measures

Primary endpoints

The two primary endpoints of this RCT are (i) the incidence of new infections during PICU stay and (ii) the duration of PICU dependency. The latter will be reported as the crude number of PICU stay days and as the time to live discharge from PICU, to account for mortality as a competing risk.

Also, the proportion of patients from the intention-to-treat population who stayed 8 days or more in PICU will be reported. This is not only reflecting the proportion of prolonged critically ill patients but also examines effects of the randomized intervention beyond the time window of the randomized intervention in PICU.

The incidence of new infections for all patients in the three centers will be scored in consensus by the same two assessors (infectious disease specialists), who are blinded for treatment allocation. This assessment is based on an *a priori* drafted protocol [19], which makes use of prescribed antibiotics and clinical infection and inflammation data.

As the timing of PICU discharge to a regular ward may be affected by the availability of beds on regular wards, which could induce bias, we *a priori* decided to analyze "time to discharge from PICU" as "time to *ready for* discharge from PICU". A patient is considered "ready for discharge" as soon as all clinical

conditions for PICU discharge have been fulfilled (no longer in need for, or at risk of, vital organ support).

Secondary safety endpoints

Secondary safety endpoints comprise (i) death during PICU stay and during the time window of the randomized intervention (up to day 8), (ii) the proportion of patients with at least one episode of severe hypoglycemia (< 40 mg/dl), (iii) in-hospital mortality and (iv) 90-day mortality. As a specific serious adverse event (SAE), hypoglycemia resistant to bolus administration of glucose during the time window of the randomized intervention will be reported for both groups.

Secondary efficacy endpoints

1. *Time to (live) discharge from hospital and duration of hospital stay*, for both the index hospitalization and total hospitalization including stay in the referred hospital.
2. *Time to final (live) weaning from mechanical respiratory support and duration of mechanical ventilation*
3. *Kidney failure*. Proportion of patients in need for renal replacement therapy (RRT) during PICU stay and the duration of RRT (for those patients requiring RRT). Also the further analysis of the maximum and daily serum level of creatinine and urea during the intervention window and during PICU-stay will be reported. Other plasma and urine markers of kidney function will be investigated.
4. *Need for pharmacological or mechanical hemodynamic support* during PICU stay and duration of such need. In addition, time to final (live) weaning from all pharmacological or mechanical hemodynamic support in PICU will be analyzed.
5. *Number of readmissions to the PICU*. The proportion of patients readmitted within 48 hours after discharge will be recorded. Also the proportion of patients readmitted to the PICU beyond 48 hours

during their index hospital stay will be reported, as these patients will have been excluded from treatment allocation and will receive standard care.

6. *Liver dysfunction*. Markers of liver function will be measured and proportion of patients with abnormal tests will be compared.
7. *Inflammation*. Effect of the intervention on inflammation will be analyzed by comparing markers of inflammation. Both peak values and time courses will be analyzed.
8. *Duration of antibiotic treatment*. The duration of antibiotic treatment (whenever given) within the intervention window and during the PICU-stay will be compared between the groups.
9. *Nutrition delivered during PICU-stay.* The macronutrients and calories administered during the intervention window and thereafter during PICU-stay will be compared between the treatment groups. Total amount of macronutrients as well as the amounts administered parenterally and enterally will be reported.
10. Structural and functional differences in muscle tissue during PICU stay. By ultrasonography, skeletal muscle thickness of the quadriceps, as a marker of muscle wasting, will be reported in a subset of patients. In addition, handgrip strength will be measured in a subset of patients older than 6 years.
11. *Intolerance to enteral feeding during PICU-stay.* Markers of tolerance to enteral feeding will be determined in a subset of patients. Markers in blood, stool and buccal swab samples will be investigated.

Further pre-planned studies (execution depending on further funding), of which the detailed protocols and the methods for statistical analysis will be reported separately, are here listed below:

1. *Direct healthcare-related costs*. Total, direct healthcare costs during index PICU stay will be compared between the treatment groups [26].

2. *Mechanistic studies*. Explanations of any observed effects of delayed administration of PN as compared with standard of care will be assessed. These will comprise, among others, metabolic, endocrine, inflammation and (epi)genetic analyses, the investigation of the role of severity of illness, the use of indirect calorimetry, the type of blood glucose management, and post-randomization factors such as type and dose of administered macronutrients, and disease evolution [27].
3. *Long-term follow-up*. This will include developmental and neurocognitive assessments, metabolic, endocrine, inflammation and (epi)genetic studies, with a healthy matched control group investigated over time in parallel.

Data collection following recruitment

All systemically applied medications received by the patients during the stay in PICU are registered. Every day the amount of kilocalories, carbohydrates, lipids and proteins delivered by either PN or EN are calculated and entered into the electronic case record form (eCRF). The need for and the number of days of mechanical ventilatory support, of mechanical and pharmacological hemodynamic support, of renal replacement therapies, days on antibiotics and days requiring a central line are recorded. Blood, urine, buccal mucosa swabs and hair samples are taken upon PICU admission and during PICU-stay. Such samples are appropriately handled (collected on ice when required) and immediately stored (at room temperature or at -20°C/-80°C as appropriate) for future measurements. Analyses on blood and urine for the primary clinical analyses include routine chemistry, hematology, and markers of inflammation. Further metabolic, endocrine, inflammatory and (epi)genetic measurements on stored samples in the context of mechanistic analyses are planned. For mechanistic and exploratory studies, ultrasound evaluation of the skeletal muscle, in combination with muscle strength measurements will be performed in a subset of patients [28-30]. Quality of life on admission and after 4-6 months is recorded

through a validated, semi-structured questionnaire, filled out by the parents, which is repeated at 2 and 4 years after enrolment in the PEPaNIC trial.

Data handling and record keeping

Data are collected electronically in an anonymized eCRF, unambiguously linked to the source file. Data are manually transferred and checked for accuracy into the eCRF by the clinical research assistants' team on a daily basis. Extensive range and consistency checks are performed by the study monitor. All original records, such as consent forms, eCRFs and relevant correspondence, will be archived at the participating centers, according to the local regulations. Vital status at 90 days (and at later follow-up times) will be recorded for all patients, by the National Death Registries. When this information is not available, vital status will be checked through the hospital information system or the regional network of pediatricians and general practitioners.

All data are stored anonymously. Investigators involved in the trial do not have direct access to the database. In addition, the study monitor has logged the use of the database. After the trial, the study monitor will store all data in a secured file that is only accessible by the study monitor himself.

Trial Organization

The sponsor (KU Leuven) provides direct access to the eCRF, the source data and the study master file for monitoring, for review by the independent ethics committee and regulatory inspection. The sponsor established an independent data safety monitoring board (DSMB). The sponsor appointed one monitor. The monitor verifies that the trial is performed in accordance to the protocol as described in the European Medicine Agency's "Note for guidance on good clinical practice CPMP/ICH/135/95." as well as the Declaration of Helsinki. Monitoring is performed and reported according to the sponsor's standard operating procedures. The clinical research team guarantees a daily follow-up of patient screening and inclusion, availability of requested clinical data in the clinical patient files and protocol compliance. Non-

compliance to the protocol and other questions or problems are reported to the study monitor and discussed with the principal investigators and trial steering committee. SAEs are reported to the study sponsor and, if needed, to the local ethics committee. The study monitor regularly provides the sponsor and the DSMB with reports on inclusions and SAEs. Regular meetings are organized with principal investigators and clinical research teams to discuss the daily progression of the PEPaNIC trial.

The protocol has been instructed in each hospital to all clinical medical and nursing staff through frequent teaching sessions and clinical feedback rounds. The protocol decision support is integrated into the PICU PDMS in Leuven and Rotterdam, facilitating the prescription of the exact amounts of PN and EN according to protocol and clinical evolution.
In order to achieve adequate participant enrolment to reach target sample size, regular meetings and site visits take place every 3 months together with the Rotterdam team and via teleconferences with the Edmonton team.

Regular data auditing is done by the administrative trial team, the DSMB and by the central independent audit procedure in place at the University Hospital of Leuven in compliance with the European Trials Directives.

Statistical analysis plan

One *consort diagram* will be reported.

Protocol compliance will be documented by comparing the actual amounts of PN and EN during the intervention window and this will be reported as absolute numbers of calories and weight units.
For the primary and secondary endpoints taking place during PICU stay all data will be available. In case of request for discontinuation of the study intervention by patients, parents or legal guardians, this

will be respected, but all data will be analyzed. In case of consent withdrawal, the parents will be asked whether the data can be used for analysis. In case this would not be allowed, all data of that patient will be removed from the database, and this will be reported in the consort diagram. At all time, the intention to treat principle will be respected and reported. No data imputation will be undertaken for any of the primary or secondary outcomes.

Variables will be *summarized* as frequencies and percentages, means and standard errors of the means, or medians and interquartile ranges, as appropriate.

Results will be analyzed with the use of chi-square testing, Student's t-test or non-parametric testing (Wilcoxon rank-sum test, Van der Waerden test or Median test), as appropriate. Kaplan-Meier plots will be used to document time-to-event effects, and the time-to-event effect size will be estimated with the use of Cox proportional-hazard analysis. All time-to-event analyses will also be performed on data censored at 90 days. As death is a competing risk for duration of care outcomes, non-survivors will be censored beyond the longest duration of such care required for survivors [19]. All outcomes will be analyzed both with and without adjustment for baseline risk factors, including the diagnostic and age groups, severity of illness, severity of nutritional risk and center. The latter is considered necessary to account for the differences among centers in nutrition given to the control group and the variation in blood glucose control targets. For these analyses, p-values will be considered significant when at or below 0.05 without correction for multiple comparisons. To assess whether any eventual impact of the intervention on the primary endpoints is affected by the baseline risk factor subgroups, interaction p-values will be calculated (logistic regression or Cox proportional hazard analysis) with a threshold for significance of interaction set at a p-value of <0.1. All analyses will be conducted on an *intention-to-treat* basis.

SAMPLE SIZE CALCULATION AND INTERIM ANALYSES

In the design phase of the PEPaNIC trial, and based on the previous adult EPaNIC trial results, the sample size (N=1440, 720 patients per arm) was determined in order to detect a reduction in the incidence of new infections during PICU stay from 20% to 15% (Absolute Risk Reduction 5%), with at least 80% one-tailed power and at least 70% two tailed power and at an alpha error of 5%. With this sample size, the trial can also detect a major safety issue, such as a doubling of the PICU mortality rate from 4% (the baseline mortality in the Leuven center) to 8% with a statistical power of 89% in a two-sided test with an alpha error of 5%. This sample size will also allow to detect a reduction in mean duration of stay in PICU of 1 day with at least 90% power (2-tailed) and 95% certainty.

Two *interim analyses* of the safety endpoints (except 90 day mortality) only were planned (after inclusion of 480 upon specific request of the DSMB, and after inclusion of 50% of the study population). It was *a priori* decided to determine the actual incidence of new infections during PICU stay in the three centers, as this was not known exactly for each of the participating centers prior to trial initiation. In order to allow statistical repowering and to judge the necessity of inclusion of more trial sites, the assessment of incidence of new infections during PICU stay in the control group took place after inclusion of 750 patients. Based on this actual incidence of new PICU infections in the control group, the hypothesized absolute risk reduction of 5% and an alpha error rate of 5%, the sample size of 1440 patients (720 patients in each arm) was found sufficiently large to yield a statistical power of 77% two-sided and of 85% one-sided. As these interim analyses did not assess any of the efficacy endpoints, no adjustments of the p-values are needed.

Discussion

The clinical evidence for the administration of PN in critically ill children is missing [18]. Thousands of children are annually exposed to this non-evidence based treatment, which is assumed to result in faster recovery (benefit). This large international RCT will help PICU physicians to get more insight on the possibility of the omission of PN during the first week of critical illness. A significant difference in the safety and/or efficacy endpoints will provide important evidence for optimizing clinical patient care. Also a neutral result will provide important insight, as this would mean that clinicians can safely withhold PN in all comparable patients during the first week of ICU stay, which would have an impact on healthcare spending in the PICU.

TRIAL STATUS

The study was initiated as planned on June 18, 2012. At the time of the safety interim analyses (after 480 and 750 study patients discharged from PICU), the DSMB advised the continuation of the trial and ratified the initial sample size of 1440 patients as adequate to test the hypothesis. On 1 December 2014, 1130 patients have been included into the PEPaNIC trial. Recruitment of the last patient is expected for October 2015.

REFERENCES

1. Joosten KF, Hulst JM (2011) Malnutrition in pediatric hospital patients: current issues. Nutrition 27:133-7.
2. Wiskin AE, Davies JH, Wootton SA, Beattie RM (2011) Energy expenditure, nutrition and growth. Arch Dis Child 96:567-72.
3. Zamberlan P, Delgado AF, Leone C, Feferbaum R, Okay TS (2011) Nutrition therapy in a pediatric intensive care unit: indications, monitoring, and complications. JPEN J Parenter Enter Nutr 35:523-9.
4. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R, Parenteral Nutrition Guidelines Working G, et al (2005) 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatric Gastroenterol Nutr 41 Suppl:S1-87.
5. Pollack MM, Ruttimann UE, Wiley JS (1985) Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. JPEN J Parenter Enter Nutr 9:309-13.
6. Mehta NM, Bechard LJ, Dolan M, Ariagno K, Jiang H, Duggan C (2011) Energy imbalance and the risk of overfeeding in critically ill children. Pediatr Crit Care Med 12:398-405.
7. Chwals WJ (1994) Overfeeding the critically ill child: fact or fantasy? New horiz 2:147-55.
8. Askanazi J, Rosenbaum SH, Hyman AI, Silverberg PA, Milic-Emili J, Kinney JM (1980) Respiratory changes induced by the large glucose loads of total parenteral nutrition. JAMA-J Am Med Assoc 243:1444-7.
9. Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, Sohn AH, Levine GL, Siegel JD, Stover BH, Jarvis WR; Pediatric Prevention Network (2002) A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. J Pediatr 140:432-8.

10. Mehta NM, Compher C (2009) A.S.P.E.N. Clinical Guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr 33:260-76.

11. van der Kuip M, Oosterveld MJ, van Bokhorst-de van der Schueren MA, de Meer K, Lafeber HN, Gemke RJ (2004). Nutritional support in 111 pediatric intensive care units: a European survey. Intensive Care Med 30:1807-13.

12. Sion-Sarid R, Cohen J, Houri Z, Singer P (2013) Indirect calorimetry: a guide for optimizing nutritional support in the critically ill child. Nutrition 29:1094-9.

13. Sundstrom M, Tjader I, Rooyackers O, Wernerman J (2013). Indirect calorimetry in mechanically ventilated patients. A systematic comparison of three instruments. Clin Nutr 32:118-21.

14. Vazquez Martinez JL, Martinez-Romillo PD, Diez Sebastian J, Ruza Tarrio F (2004) Predicted versus measured energy expenditure by continuous, online indirect calorimetry in ventilated, critically ill children during the early postinjury period. Pediatr Crit Care Med. 5:19-27.

15. Hardy CM, Dwyer J, Snelling LK, Dallal GE, Adelson JW (2002) Pitfalls in predicting resting energy requirements in critically ill children: a comparison of predictive methods to indirect calorimetry. Nutr Clin Pract: official publication of the American Society for Parenteral and Enteral Nutrition. 17:182-9.

16. White MS, Shepherd RW, McEniery JA (2000). Energy expenditure in 100 ventilated, critically ill children: improving the accuracy of predictive equations. Crit Care Med 28:2307-12.

17. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C, ESPEN (2009) ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr 28:387-400.

18. Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, Hartling L (2009) Nutritional support for critically ill children. Cochrane Database Syst Rev:CD005144.

19. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, Van Cromphaut S, Ingels C, Meersseman P, Muller J, Vlasselaers D, Debaveye Y, Desmet L, Dubois J, Van Assche A, Vanderheyden S, Wilmer A, Van den Berghe G (2011) Early versus late parenteral nutrition in critically ill adults. N Engl J Med 365:506-17.

20. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, Davies AR, O'Leary M, Solano T, Peake S; Early PN Investigators of the ANZICS Clinical Trials Group (2013) Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA-J Am Med Assoc 309:2130-8.

21. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, Thibault R, Pichard C (2013) Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 381:385-93.

22. Hulst JM, Zwart H, Hop WC, Joosten KF (2010) Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. Clin Nutr 29:106-11.

23. Schofield WN (1985) Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 39 Suppl:5-41.

24. Vlasselaers D. Milants I, Desmet L, Vanhorebeek I, van den Heuvel I, Mesotten D, Casaer MP, Meyfroidt G, Ingels C, Muller J, Van Crophaut S, Schetz M, Van den Berghe G.(2009) Intensive insulin therapy for patients in pediatric intensive care: a prospective, randomised controlled study. Lancet Feb 14;373(9663):547-56

25. Verhoeven JJ, Brand JB, van de Polder MM, Joosten KF (2009) Management of hyperglycemia in the pediatric intensive care unit; implementation of a glucose control protocol. Pediatr Crit Care Med 10:648-52.

26. Vanderheyden S, Casaer MP, Kesteloot K, Simoens S, De Rijdt T, Peers G, Wouters PJ, Coenegrachts J, Grieten T, Polders K, Maes A, Wilmer A, Dubois J, Van den Berghe G,

Mesotten D (2012) Early versus late parenteral nutrition in ICU patients: cost analysis of the EPaNIC trial. Crit Care 16:R96.

27. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G (2013) Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med 187:247-55.

28. Heckmatt JZ, Pier N, Dubowitz V (1988) Measurement of quadriceps muscle thickness and subcutaneous tissue thickness in normal children by real-time ultrasound imaging. J Clinical Ultrasound 16:171-6.

29. Williams S, Horrocks IA, Ouvrier RA, Gillis J, Ryan MM (2007) Critical illness polyneuropathy and myopathy in pediatric intensive care: A review. Pediatr Crit Care Med 8:18-22.

30. Chiba T, Lloyd DA, Bowen A, Condon-Meyers A (1989) Ultrasonography as a method of nutritional assessment. JPEN J Parenter Enter Nutr 13:529-34.

7. The Pediatric Early versus Late Parenteral Nutrition in Critical Illness

Adapted from:

Fivez T , Kerklaan D*, Mesotten D*, Verbruggen SC*, Wouters PJ, Vanhorebeek I, Debaveye Y, Vlasselaers D, Desmet L, Casaer MP, Guerra GC, Hanot J, Joffe A, Tibboel D, Joosten K, Van den Berghe G.. The Pediatric Early versus Late Parenteral Nutrition in Critically Ill Children. NEJM (in press)*

** Equal contribution, alphabetical order*

Abstract

Background

In critically ill children, the impact of early parenteral nutrition on clinical outcomes is unclear. In adults, recent trials have questioned the benefit of early parenteral nutrition.

Methods

This multi-center randomized controlled trial of 1440 critically ill children investigated whether withholding parenteral nutrition for 1 week (late parenteral nutrition) in the pediatric intensive care unit (PICU), while providing similar fluid loading, is clinically superior to early parenteral nutrition. In 723 patients in the early parenteral nutrition group, parenteral nutrition was initiated within 24 hours, whereas the 717 patients in the late parenteral nutrition group did not receive parenteral nutrition before day 8. In both groups, enteral nutrition was attempted early, and intravenous micronutrients were given.

Results

Whereas mortality rates were similar, late parenteral nutrition reduced the proportion of patients with a new infection from 18.5% with early parenteral nutrition to 10.7% [Adjusted Odds Ratio 0.48 (95%CI 0.35-0.66)]. Late parenteral nutrition also reduced the duration of PICU stay from a mean±SEM 9.2±0.8 days to 6.5±0.4 days, with a higher likelihood of an earlier live discharge from PICU at any time [Adjusted Hazard Ratio 1.23 (1.11-1.37)]. Late parenteral nutrition reduced the duration of mechanical ventilatory support (P=0.001), the proportion of patients on renal replacement therapy (P=0.038) and the duration of hospital stay (P=0.001). Late parenteral nutrition lowered plasma gamma-glutamyltransferase (P=0.001) and alkaline-phosphatase (P=0.036) concentrations and increased plasma bilirubin (P=0.004) and C-reactive-protein (P=0.006).

Conclusion

In critically ill children, omitting parenteral nutrition for 1 week was clinically superior to providing early parenteral nutrition.

ClinTrials.gov Identifier NCT01536275

Background

Critically ill children cannot be fed normally by mouth, which often results in a pronounced macronutrient deficit after a few days. This macronutrient deficit has been associated with infections, weakness, prolonged mechanical ventilation and delayed recovery.[1-3] In order to prevent or reduce this macronutrient deficit, current guidelines, largely based on small studies with surrogate endpoints and expert opinion, advise that nutritional support be initiated soon after admission to the pediatric intensive care unit (PICU).[4-6] The preferred route for providing nutrition in PICU is via a nasogastric tube[7] but enteral nutrition is often delayed or interrupted.[8,9] Children require relatively more macronutrients than adults as nutrition should equal basic metabolic needs and allow for growth. Hence, current standard of pediatric intensive care is to meet these requirements early.[7,10] When enteral nutrition fails, parenteral nutrition is advised[5,6] but concerns about parenteral nutrition overdosing[11] explain why current nutritional practices in PICUs vary.[8]

Randomized controlled trials (RCTs) that address, with adequate statistical power, the impact of parenteral nutrition on clinical outcomes in critically ill children are currently lacking.[12] In critically ill adults, recent large RCTs have questioned the benefit of early parenteral nutrition.[13-15] Therefore, in this international multicenter RCT, we investigated whether a strategy of withholding parenteral nutrition up to day 8 in the PICU (late parenteral nutrition) is clinically superior to the current practice of early parenteral nutrition.

Methods

Study Design and Oversight

The Pediatric Early versus Late Parenteral Nutrition In Critical Illness (**PEPaNIC**) study was a multicenter prospective, randomized, controlled, parallel-group superiority trial (ClinTrials.gov NCT01536275).[16] The institutional/national ethical review boards of the participating sites approved the study protocol and the consent forms. The study protocol and statistical analysis plan are available at www.NEJM.org, and have been reported.[16] The first and last authors vouch for the fidelity of the study to the protocol.

Patients

From June 18, 2012 through July 27, 2015 all children (term newborn to 17 years old), who were admitted to one of the participating PICUs were eligible for inclusion, if a PICU stay of minimal 24 hours was expected, a STRONGkids nutritional risk score of two points or more was present,[17] and if none of the exclusion criteria were met (Supplementary_Appendix,_Table_1). *Informed consent* was requested from the parents or legal guardians prior to elective admissions. For emergency admissions, the parents or legal guardians were approached for informed consent within 24 hours after PICU admission.

Per center, consecutive, eligible patients were randomly assigned to one of the two treatment arms in a 1-to-1 ratio. Concealment of the allocation to the randomized treatment was ensured by a central computerized randomization system. The randomization was stratified, in permuted blocks of 10, by age (<1 and ≥1 year) and diagnosis upon admission (medical–neurological, medical-other, surgical-cardiac and surgical-other). The block size was unknown to the medical and research team.

Outcome assessors and investigators not directly involved in patient intensive care were blinded to treatment allocation.

The Independent Data and Safety Monitoring Board (DSMB) planned to perform 2 interim analyses of the safety endpoints, 1 after inclusion of 480 patients and a second after inclusion of 50% of all patients. The DSMB advised that recruitment could be continued to completion.

Study Procedures

All participating centers used early parenteral nutrition as the standard of care. In patients assigned to the *early parenteral nutrition* group (*control group*), parenteral nutrition was initiated within 24 hours after PICU admission in a dose and composition that varied according to local guidelines (Supplementary Appendix, _Table_2)[16] and that supplemented any enteral nutrition up to local macronutrient and caloric targets (Supplementary_Appendix, _Table_3).

In patients allocated to the *late parenteral nutrition* group (*intervention group*), parenteral nutrition was withheld up to the morning of day 8 in the PICU. To match the fluid administration of the control group, taking into account the volume of enteral nutrition delivered, a mixture of dextrose 5% and saline was provided.[16] When blood glucose concentrations spontaneously dropped below 50 mg/dL in the late parenteral nutrition group, dextrose 5% was switched to 10% until blood glucose exceeded 80 mg/dL and remained stable.[16]

In both treatment groups equally, enteral nutrition was initiated early and increased according to local guidelines. Both groups also received intravenous micronutrients (trace elements, minerals and vitamins) from day 2 onwards until enteral nutrition reached 80% of the caloric targets. From the morning of day 8 in PICU onward, supplementary parenteral nutrition was provided for those patients in both groups who were not yet receiving 80% of the caloric target enterally. In Leuven, insulin infusion was started in both groups to target blood glucose concentrations of 50-80 mg/dL for infants (aged <1y) and 70-100 mg/dL for children (aged ≥ 1 year). In Rotterdam, all patients received insulin infusion to

target blood glucose concentrations of 72-145 mg/dL, except for patients with traumatic brain injury for whom the target was 108-145 mg/dL. In Edmonton, patients received insulin infusion when blood glucose levels exceeded 180 mg/dL.

Data Collection

All patient data were stored in a logged database that was closed 90 days after inclusion of the last patient. At baseline, the two randomization groups were comparable (Table 1). As the Pediatric Risk of Mortality could not be used as a baseline severity of illness score, given that treatment allocation expectedly affected the highest blood glucose concentration during the first 24h, the Pediatric Logistic Organ Dysfunction (PELOD) score of the first 24h was used instead. The admission risk of malnutrition was quantified with use of the STRONGkids score, dichotomized for "medium risk" (score 2 and 3) and "high risk" (score 4 and 5).[17] Presence of an infection upon PICU admission and of any new infection acquired after randomization was judged in consensus by two infectious disease specialists who were blinded for treatment allocation, with use of an *a priori*-drafted protocol (Supplementary_Appendix,_Table_4).[13] Daily records were kept regarding all intensive care procedures, treatments, nutrition and laboratory results. Information on vital status at 90 days was obtained from National Death Registries, hospital information systems and regional networks of pediatricians and general practitioners.

Outcome Measures

Primary Endpoints

The two primary endpoints were new infection acquired during PICU stay and the duration of PICU dependency, adjusted for 5 predefined baseline risk factors (diagnostic groups, age group, severity of illness, severity of nutritional risk and center).[16] For patients with a new infection, the duration of antibiotic treatment was compared. The duration of PICU dependency was quantified as the number of

PICU days and as time to live discharge from PICU to account for mortality as a competing risk. Discharge from PICU was *a priori* defined as the moment when patients were ready for PICU discharge (no longer requiring, or at risk of requiring, vital organ support).[16]

Secondary Safety Endpoints

Death during the time window of the randomized intervention (first 7 days in PICU), during PICU stay, during index hospitalization and at the 90-day landmark, the number of patients with hypoglycemia (below 40 mg/dL) and the number of readmissions to the PICU within 48h were secondary safety endpoints.

Secondary Efficacy Endpoints

Secondary efficacy outcomes were time to final (live) weaning from mechanical ventilatory support, duration of pharmacological and/or mechanical hemodynamic support, proportion of patients receiving renal replacement therapy (RRT), markers of liver dysfunction and inflammation and time to (live) discharge from the hospital.

Statistical Analyses

The sample size (N=1440, 720 patients per arm) was calculated to detect a 5% absolute reduction in the proportion of patients with a new infection (from an estimated baseline of 20%) with at least 70% two-tailed power and an alpha error of 5%.

All analyses were conducted on an intention-to-treat basis.

Variables were summarized as frequencies and percentages, medians and interquartile ranges, or means and standard errors (SEM). Univariable comparisons were done with use of the chi-square test

(Fisher Exact) and by the Wilcoxon rank-sum test. Kaplan-Meier plots were used to illustrate time-to-event effects with univariable significance analyzed by log-rank testing. The time-to-event effect size was estimated with use of Cox Proportional Hazard Analysis, censored at 90 days. To take into account death as a competing risk for duration of care outcomes, non-survivors were censored beyond all survivors at 91 days. These time-to-event outcomes were assessed univariably and with adjustment for the baseline risk factors (diagnostic groups, age group, severity of illness, severity of nutritional risk and center). The adjusted multivariable analysis of the impact of the intervention on dichotomized outcomes was done with Logistic Regression Analysis.

All P-values were 2-sided and considered significant when <0.05. No corrections for multiple comparisons were done. As the interim analyses did not assess efficacy endpoints, no adjustment of the P-value threshold for significance was required.

To assess whether the impact of the intervention on the primary endpoints was affected by the baseline risk factor subgroups, interaction P-values were calculated (Multivariable Logistic Regression Analyses and Multivariable Cox Proportional Hazard Analyses) with a threshold for significance of interaction set at a P-value of <0.1.

All analyses were performed with the use of JMP software version 11.2.0 (SAS Institute).

Results

Study Intervention

A total of 1440 patients underwent randomization and were included in the analysis (Fig.1). Caloric and macronutrient intake per day up to day 16 in the PICU, illustrating protocol compliance, is shown in Figure 2 (Supplementary_Appendix,_Fig.S1_Fig.S2).

Primary Outcomes

With late parenteral nutrition, the proportion of patients who acquired a new infection was an absolute 7.8% (95% CI 4.2%-11.4%) lower than with early parenteral nutrition (Table 2) [Adjusted Odds Ratio (OR) of 0.48 (95% CI 0.35-0.66)] (Table 3). This was mostly attributable to fewer patients acquiring an airway or blood stream infection in the late parenteral nutrition group (Table 2). Late parenteral nutrition also reduced the duration of stay in the PICU by a mean 2.7 (95% CI 1.3-4.3) days (Table 2), with a higher likelihood of an earlier live discharge from PICU at any time [Adjusted Hazard Ratio (HR) of 1.23 (95% CI 1.11-1.37)] (Table 2, Fig. 3; Supplementary_Appendix,_Fig.3, Supplementary_Appendix,_Table_5). There were no significant (P<0.1) interactions between treatment allocation and any of the predefined risk factors (Supplementary_Appendix,_Table_6). However, the P-value for interaction between randomized treatment allocation and the nutritional risk was 0.1 for new infections, with a greater reduction of infections with late parenteral nutrition in the high nutritional risk group [OR 0.28 (95% CI 0.10-0.70)] than in the medium nutritional risk group [OR 0.54 (0.38-0.76)]. There was also a higher likelihood of an earlier live discharge from PICU with late parenteral nutrition in the high nutritional risk group [HR 1.61 (95% CI 1.12-2.31)] than in the medium nutritional risk group [HR 1.19 (95% CI 1.06-1.33)] (interaction P=0.1).

There was also no significant interaction between treatment allocation and age group. A post-hoc subgroup analysis of the 209 term neonates aged less than 4 weeks at time of inclusion revealed that

the benefits of late parenteral nutrition were similar or larger than for children aged 4 weeks or more [OR for new infections 0.47 (95% CI 0.22-0.95) for neonates versus 0.48 (95% CI 0.33-0.69) for older children, interaction P=0.9; likelihood of earlier live discharge from PICU HR 1.73 (95% CI 1.27-2.35) for neonates versus 1.17 (95% CI 1.04-1.31) for older children, interaction P=0.033].

The impact of late PN on the primary outcomes was unaltered after adjusting for the amount of enteral nutrition (Supplementary_Appendix,_Table_7).

Secondary Safety Outcomes

Mortality rate was similar in both groups for all predefined time horizons (Table 2, Fig. 3). The proportion of patients with an episode of hypoglycemia below 40 mg/dL was higher in the late parenteral nutrition than in the early parenteral nutrition group (Table 2). Adjusting for hypoglycemia did not alter the effect size of late parenteral nutrition on the primary outcomes [OR for new infection 0.45 (95%CI 0.32-0.62) and likelihood of an earlier live discharge from PICU adjusted hazard ratio of 1.26 (95% CI 1.13-1.41)] (Supplementary_Appendix,_Table_7). Readmission to PICU within 48h and occurrence of serious adverse events were similar for the 2 randomization groups (Table 2).

Secondary Efficacy Outcomes

Late parenteral nutrition reduced the duration of mechanical ventilatory support and increased the likelihood of live weaning thereof (Table 2; Supplementary_Appendix,_Table_5), whereas the duration of hemodynamic support was unaltered. After adjustment for predefined risk factors, late parenteral nutrition also reduced the odds for renal replacement therapy (Table 2; Supplementary_Appendix,_Table_5). With late parenteral nutrition, the plasma total bilirubin levels peaked higher than with early parenteral nutrition during the intervention window (Table 2) and during the duration of PICU stay (Supplementary_Appendix,_Table_8), while plasma gamma-glutamyltransferase and alkaline phosphatase levels peaked higher with early parenteral nutrition (Table

2). Other liver tests were unaltered (Table 2). Despite fewer new infections with late parenteral nutrition, plasma CRP concentrations peaked higher during the intervention window (Table 2).

Duration of stay in the *index* hospital was a mean 4.1 (95% CI 1.4-6.6) days shorter, and the likelihood of an earlier live discharge from hospital was higher [Adjusted HR 1.19 (95% CI 1.07-1.33)] in the late parenteral nutrition group (Table 2, Fig. 3; Supplementary_Appendix,_Fig.3, Supplementary_Appendix,_Table_5). This effect of late parenteral nutrition remained significant when taking into account any eventual additional stay in a *transferral* hospital (Table 2, Fig. 3; Supplementary_Appendix,_Fig.3, Supplementary_Appendix,_Table_5).

Adjusting for hypoglycemia or for the amount of enterally administered nutrition did not alter the impact of late parenteral nutrition on any of the secondary outcomes (Supplementary_Appendix,_Table_7).

Discussion

We here demonstrated that withholding parenteral nutrition for one week in the PICU was clinically superior to early provision of parenteral nutrition, with fewer new infections, shorter duration of intensive care dependency and a shorter hospital stay.

The clinical superiority of late parenteral nutrition was present irrespective of the diagnosis, severity of illness, nutritional risk and age of the child. The observation that critically ill children at highest nutritional risk benefited the most from withholding early parenteral nutrition was unexpected. However, this finding was reinforced by an apparently greater benefit of not providing parenteral nutrition early to critically ill term neonates than to older children. Indeed, immediate initiation of nutrition is advised for neonates because they are considered to have less metabolic reserve.[7]

Late parenteral nutrition exerted its benefits irrespective of the variability in nutritional care and blood glucose management across participating centers. Late parenteral nutrition increased hypoglycemia but this did not affect its impact on outcome. Such brief episodes of hypoglycemia during pediatric critical illness or in premature/mature newborns also did not negatively affect long-term neurocognitive outcomes in earlier studies.[18-20]

The finding that late parenteral nutrition substantially reduced new infections but increased inflammation as indicated by plasma CRP illustrates the limitation of surrogate endpoints for trials.[21-25] As in a previous adult study, late parenteral nutrition reduced plasma gamma-glutamyltransferase and alkaline phosphatase also in children, suggestive of less cholestasis.[13,26,27] However, late parenteral nutrition increased plasma bilirubin in these critically ill children as it did in adult patients, further supporting the concept that elevated plasma bilirubin in response to critical illness may be partially adaptive.[28]

Underlying mechanisms of the clinical benefits observed with accepting a substantial macronutrient deficit early during critical illness in children remain speculative. Preservation of autophagy may play a

role given its importance for innate immunity and for quality control in cells with a long half-life such as myofibers.[29-31]

A limitation of this study is that patients, their parents and the intensive care providers were aware of the treatment allocation. However, outcome assessors and caregivers on the pediatric wards were blinded. The strength of this study is the external validity, given the multicenter study design.

In conclusion, In critically ill children, omitting parenteral nutrition for 1 week while giving micronutrients intravenously was clinically superior to providing early parenteral nutrition to supplement insufficient enteral nutrition.

FIGURE LEGENDS

Figure 1. Consort Diagram

Patients were excluded for several reasons, as listed in Supplementary_Table_1. NICU stands for Neonatal Intensive Care Unit, PICU for Pediatric Intensive Care Unit, PN for Parenteral Nutrition and DNR for a “Do Not Resuscitate” order.

Figure 2. Caloric and Macronutrient Intake

Daily amount of energy in kcal/day, and the daily amounts of substrates in g/day, for the first 16 days of pediatric intensive care (PICU) stay provided by the enteral route, the parenteral route or both (total). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the late parenteral nutrition (PN) group; the blue bars represent the early PN group.

Figure 3. Kaplan-Meier plots for the time to discharge from the PICU and the hospital and for survival up to 90 days

The panels A-C represent the cumulative proportions of patients discharged from the PICU (A) and from the hospital [index (B); total (C)]. Data for surviving patients were censored at 90 days while non-survivors were censored at time of death. For sake of clarity, only the first 30 days are shown in panels A-C. Panel D illustrates survival up to 90 days. The red lines represent the late PN group; the blue lines represent the early PN group. *univariable log-rank P-value; $ P-value adjusted in multivariable analysis.

FIGURE 1

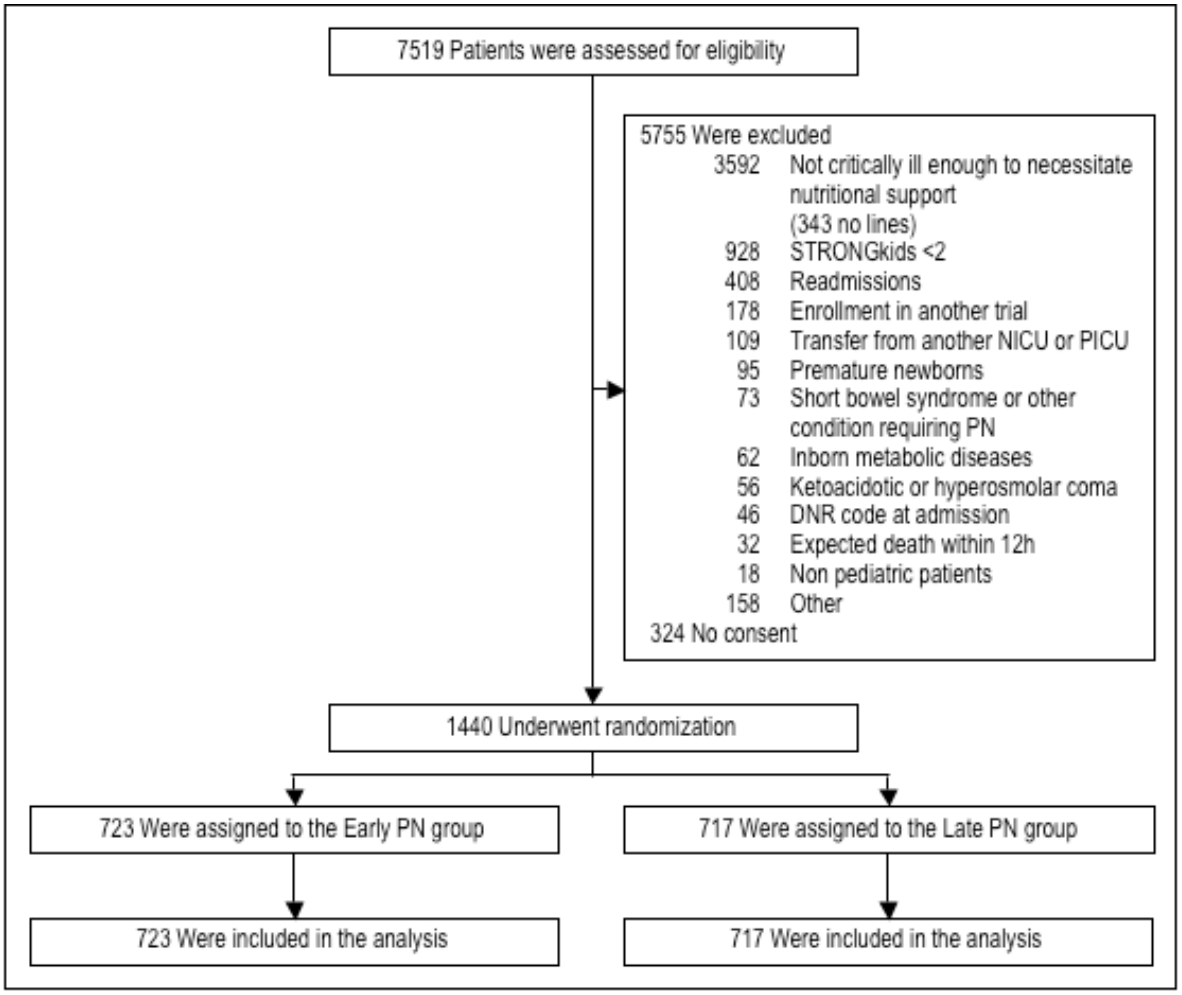

7519 Patients were assessed for eligibility
5755 Were excluded
3592 Not critically ill enough to necessitate nutritional support (343 no lines)
928 STRONGkids <2
408 Readmissions
178 Enrollment in another trial
109 Transfer from another NICU or PICU
95 Premature newborns
73 Short bowel syndrome or other condition requiring PN
62 Inborn metabolic diseases
56 Ketoacidotic or hyperosmolar coma
46 DNR code at admission
32 Expected death within 12h
18 Non pediatric patients
158 Other
324 No consent
1440 Underwent randomization
723 Were assigned to the Early PN group
717 Were assigned to the Late PN group
723 Were included in the analysis
717 Were included in the analysis

FIGURE 2

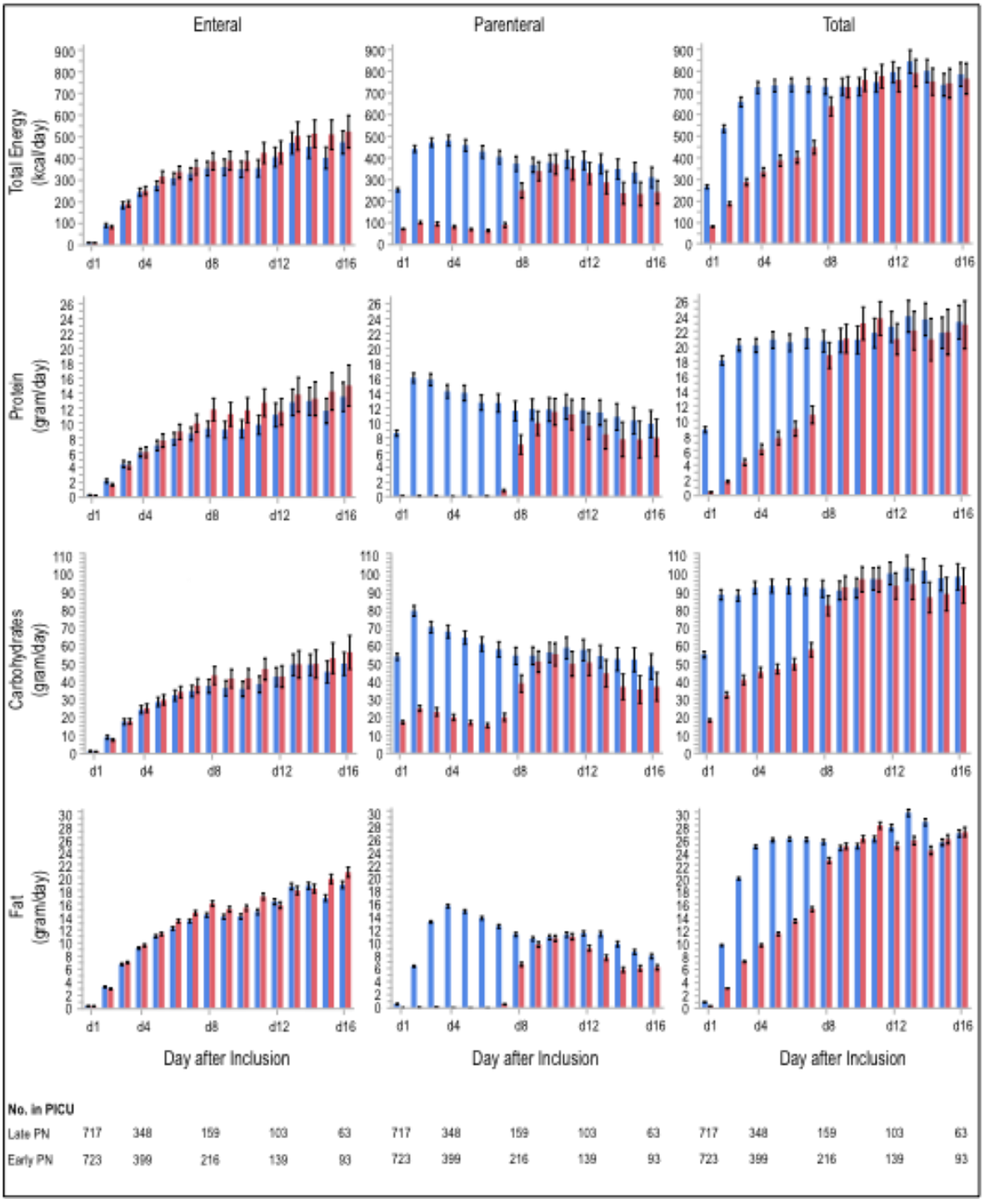

Enteral
Parenteral
Total
Total Energy (kcal/day)
Protein (gram/day)
Carbohydrates (gram/day)
Fat (gram/day)
d1
d4
d8
d12
d16
Day after Inclusion
No. in PICU
Late PN 717 348 159 103 63 717 348 159 103 63 717 348 159 103 63
Early PN 723 399 216 139 93 723 399 216 139 93 723 399 216 139 93

FIGURE 3

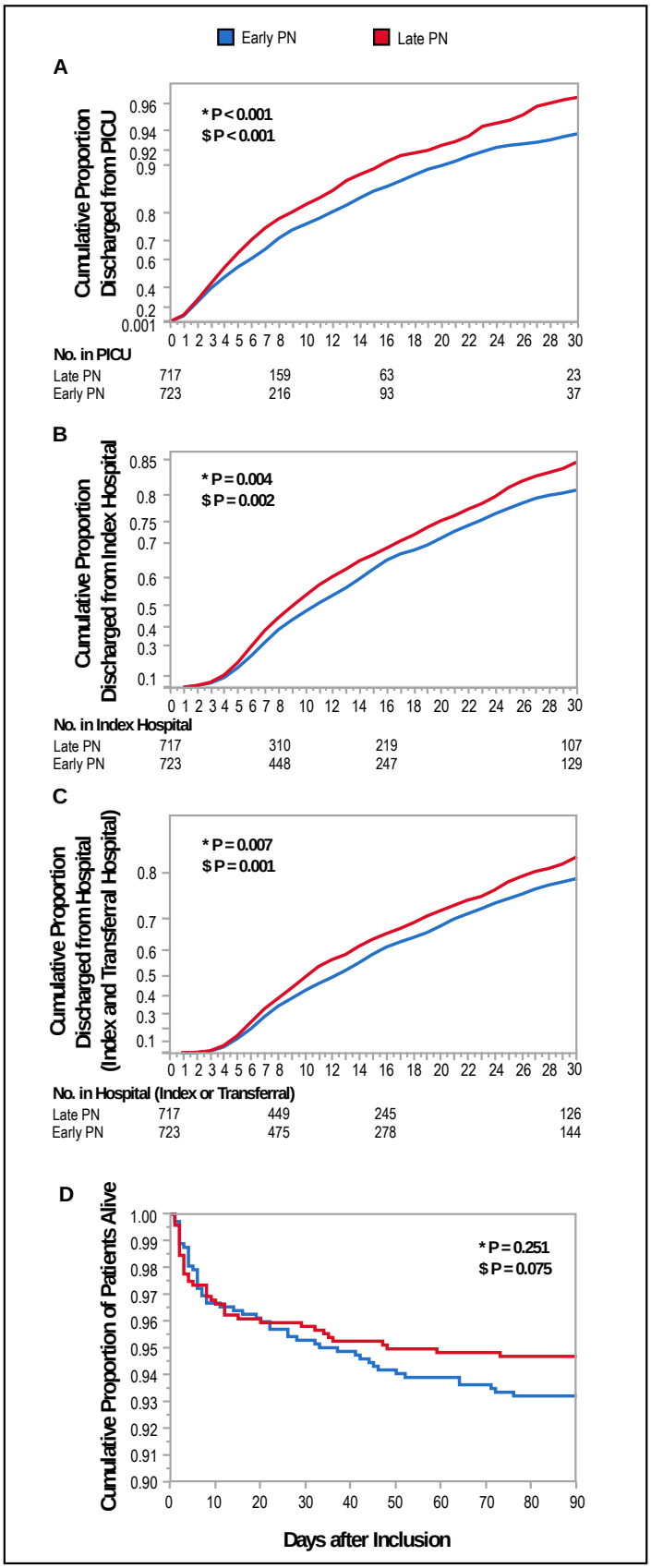

Early PN
Late PN
A
Cumulative Proportion Discharged from PICU
*P<0.001
$P<0.001
No. in PICU
Late PN 717 159 63 23
Early PN 723 216 93 37
B
Cumulative Proportion Discharged from Index Hospital
*P=0.004
$P=0.002
No. in Index Hospital
Late PN 717 310 219 107
Early PN 723 448 247 129
C
Cumulative Proportion Discharged from Hospital (Index and Transferral Hospital)
*P=0.007
$P=0.001
No. in Hospital (Index or Transferral)
Late PN 717 449 245 126
Early PN 723 475 278 144
D
Cumulative Proportion of Patients Alive
*P=0.251
$P=0.075
Days after Inclusion

TABLE 1

There were no statistically significant differences in baseline characteristics between treatment groups.

Table 1. Baseline Characteristics		
	Early PN	**Late PN**
Total number of patients	723	717
Age - yr (median - IQR)	1.4 (0.3-6.1)	1.5 (0.2-7.2)
Infant (age <1 year) No (%)	328 (45.4)	325 (45.3)
Male - No (%)	415 (57.4)	415 (57.9)
Weight - kg (median - IQR)	10.0 (4.8-20.0)	10.3 (4.5-21.5)
SD score* (median - IQR)	-0.5 (-1.4-0.5)	-0.4 (-1.4-0.5)
Height - cm (median - IQR)	80 (58-113)	80 (56-120)
SD score* (median - IQR)	-0.3 (-1.5-0.8)	-0.3 (-1.4-0.8)
BMI SD score* (median - IQR)	-0.5 (-1.5-0.5)	-0.5 (-1.6-0.6)
STRONGkids		
Medium risk (score 2 or 3) - No (%)	644 (89.1)	644 (89.8)
High risk (score 4 or 5) - No (%)	79 (10.93)	73 (10.18)
PELOD first 24h in PICU (median - IQR)	21 (11-31)	21 (11-31)
Emergency Admission - No (%)	383 (53.0)	400 (55.8)
Diagnostic Groups - No (%)		
Surgical		
Abdominal	53 (7.3)	60 (8.4)
Burns	5 (0.7)	5 (0.7)
Cardiac	279 (38.5)	268 (37.3)
Neurosurgery – Traumatic Brain Injury	63 (8.7)	53 (7.3)
Thoracic	34 (4.7)	27 (3.8)
Transplantation	7 (1.0)	17 (2.4)
Trauma/Orthopedic	28 (3.9)	26 (3.6)
Other	21 (2.9)	27 (3.8)
Medical		
Cardiac	30 (4.2)	31 (4.3)
Gastrointestinal/Hepatic	2 (0.3)	4 (0.6)
Oncologic/Hematologic	8 (1.1)	7 (1.0)
Neurologic	51 (7.1)	52 (7.3)
Nephrologic	1 (0.1)	1 (0.1)
Respiratory	99 (13.7)	96 (13.4)
Other	42 (5.8)	43 (6.0)
Admission mechanical ventilation - No (%)	639 (88.4)	622 (86.8)
Admission ECMO or other assist device – No (%)	19 (2.6)	25 (3.5)
Admission with infection – No (%)	287 (39.9)	271 (37.8)

PN stands for Parenteral Nutrition, IQR for Interquartile Range, PELOD for PEdiatric Logistic Organ Dysfunction, PICU for Pediatric Intensive Care Unit, BMI for Body Mass Index, *Age- and gender specific standard deviation (SD) scores were calculated using WHO reference data (http://www.who.int/growthref/en/).

TABLE 2

	Early PN N=723	Late PN N=717	P Value	OR or HR adjusted[º] (95% CI) Late PN vs. Early PN	P Value
Primary Outcomes					
Patients with New Infections – No (%)	134 (18.5)	77 (10.7)	<0.001	0.48 (0.35-0.66)	< 0.001
Airway	59 (8.2)	30 (4.2)	0.002		
Blood Stream	23 (3.2)	10 (1.4)	0.03		
Urinary Tract	7 (1.0)	2 (0.28)	0.17		
Central Nervous System	3 (0.4)	2 (0.3)	1.00		
Soft Tissue	7 (1.0)	4 (0.6)	0.54		
Other Focus	5 (0.7)	8 (1.1)	0.42		
No Focus Identified	30 (4.1)	21 (2.9)	0.25		
Total Duration Antibiotic Treatment when Infected – Days*	21.3 (3.1)	17.4 (1.9)	0.77		
Total Duration of Stay in PICU[§]					
Days*	9.2 (0.8)	6.5 (0.4)	0.002	1.23 (1.11-1.37)	< 0.001
Patients Requiring at least 8 Days in PICU - No (%)	216 (29.88)	159 (22.2)	<0.001		
Secondary Safety Outcomes					
Non-survivors - No (%)					
Within 8 Days in PICU	21 (2.9)	19 (2.6)	0.87	0.73 (0.34-1.51)	0.39
During PICU Stay	36 (5.0)	32 (4.5)	0.70	0.73 (0.42-1.28)	0.27
During Hospital Stay	44 (6.1)	37 (5.2)	0.49	0.72 (0.43-1.19)	0.20
Within 90 days after enrollment	49 (6.8)	38 (5.3)	0.26	0.64 (0.39-1.05)	0.07
Patients with Hypoglycemia <40 mg/dL During Intervention - No (%)	35 (4.8)	65 (9.1)	0.001		
SAE (hypoglycemia refractory to treatment for 2h) - No (%)	0 (0.000)	1 (0.001)	1.00		
Readmissions to PICU within 48h - No (%)	9 (1.2)	13 (1.8)	0.39		
Secondary Efficacy Outcomes					
Duration of Mechanical Ventilatory Support - Days*	6.4 (0.7)	4.4 (0.3)	0.01	1.19 (1.07-1.32)	0.001
Duration of Hemodynamic Support - Days *	3.0 (0.3)	2.4 (0.2)	0.35		
Kidney Failure					
Renal Replacement Therapy - No (%)	26 (3.6)	18 (2.5)	0.28	0.49 (0.24- 0.96)	0.03
Liver Dysfunction (during intervention window)*					
Highest plasma Bilirubin - mg/dL (N=1252)	1.4 (0.1)	1.7 (0.1)	0.004		
Highest plasma Alkaline Phosphatase- IU/L (N=1234)	171 (3)	171 (5)	0.03		
Highest plasma GGT - IU/L (N=1217)	59 (6)	45 (3)	0.001		
Highest plasma ALT - IU/L (N=1260)	72 (8)	113 (20)	0.64		
Highest plasma AST - IU/L (N=1259)	179 (26)	263 (48)	0.69		
Inflammation (during intervention window)*					
Highest plasma CRP - mg/L (N=1296)	79 (4)	90 (4)	0.006		
Duration of Stay in Hospital*					
Index Hospital - Days	21.3 (1.3)	17.2 (1.0)	0.005	1.19 (1.07-1.33)	0.001
Total (Index + Transferral Hospital) - Days	22.6 (1.3)	18.6 (1.0)	0.010	1.21 (1.08-1.34)	< 0.001

No censoring was applied for the unadjusted comparisons of duration of care outcomes. All adjusted duration of care outcomes were censored at 90 days with non-survivors censored at 91 days.
PN stands for Parenteral Nutrition, PICU for Pediatric Intensive Care Unit, GGT for Gamma-Glutamyltransferase, ALT for Alanine Aminotransferase, AST for Aspartate Aminotransferase, CRP for C-Reactive Protein, OR for Odds Ratio, HR for Hazard Ratio, 95% CI for 95% confidence intervals,

*Mean (Standard Error of the Mean).

[$]The duration of stay in the PICU was defined as the time from admission of patients until patients were ready for discharge. Patients were considered ready for discharge as soon as all clinical conditions for ICU discharge were fulfilled (i.e., no longer requiring, or at risk of requiring, vital-organ support)
[º]Adjusted for the following risk factors: center, age group, diagnosis group, PELOD score (first 24h) and STRONGkids category

References

1. Pollack MM, Ruttimann UE, Wiley JS. Nutritional depletions in critically ill children: associations with physiologic instability and increased quantity of care. JPEN J Parenter Enteral Nutr 1985;9:309-13.
2. Mehta NM, Bechard LJ, Cahill N, et al. Nutritional practices and their relationship to clinical outcomes in critically ill children--an international multicenter cohort study*. Crit Care Med 2012;40:2204-11.
3. de Betue CT, van Steenselen WN, Hulst JM, et al. Achieving energy goals at day 4 after admission in critically ill children; predictive for outcome? Clin Nutr 2015;34:115-22.
4. Joffe A, Anton N, Lequier L, et al. Nutritional support for critically ill children. Cochrane Database Syst Rev 2009:CD005144.
5. Koletzko B, Goulet O, Hunt J, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41 Suppl 2:S1-87.
6. Mehta NM, Compher C, Directors ASPENBo. A.S.P.E.N. Clinical Guidelines: nutrition support of the critically ill child. JPEN J Parenter Enteral Nutr 2009;33:260-76.
7. Goday PS, Mehta NM. Pediatric Critical Care Nutrition: McGraw-Hill Companies, Inc.; 2015.
8. Kerklaan D, Fivez T, Mehta NM, et al. Worldwide survey of nutritional practices in pediatric intensive care units. Pediatr Crit Care Med 2015 Oct 26. [Epub ahead of print]
9. Mehta NM, McAleer D, Hamilton S, et al. Challenges to optimal enteral nutrition in a multidisciplinary pediatric intensive care unit. JPEN J Parenter Enteral Nutr 2010;34:38-45.
10. Mehta NM. The critically ill child. In: Duggan C, Watkins J, Walker WA, eds. Nutrition in Pediatrics, 4th ed. Hamilton, Ontario, Canada: BC Decker Inc; 2008.
11. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009;361:1088-97.

12. Fivez T, Kerklaan D, Mesotten D, Verbruggen SC, Joosten KF, Greet Van den Berghe G. Evidence for the Use of Parenteral Nutrition in the Pediatric Intensive Care Unit. Clin Nutr 2015 Nov 23. pii: S0261-5614(15)00324-6. doi: 10.1016/j.clnu.2015.11.004. [Epub ahead of print].
13. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med 2011;365:506-17.
14. Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA 2013;309:2130-8.
15. Heidegger CP, Berger MM, Graf S, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet 2013;381:385-93.
16. Fivez T, Kerklaan D, Verbruggen S, et al. Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial. Trials 2015;16:202.
17. Hulst JM, Zwart H, Hop WC, Joosten KF. Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. Clin Nutr 2010;29:106-11.
18. Mesotten D, Gielen M, Sterken C, et al. Neurocognitive development of children 4 years after critical illness and treatment with tight glucose control: a randomized controlled trial. JAMA 2012;308:1641-50.
19. Mckinlay CJ, Alsweiler JM, Ansell JM, et al. Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years. N Engl J Med 2015;373:1507-18.
20. Tin W, Brunskill G, Kelly T, Fritz S. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. Pediatrics 2012;130:e1497-503.

21. Chaloupecky V, Vislocky I, Pachl J, Sprongl L, Svomova V. The effect of early parenteral nutrition on amino acid and protein metabolism in infants following congenital heart disease surgery in extracorporeal circulation. Cor et Vasa 1994;36:26-34.

22. Chaloupecky V, Hucin B, Tlaskal T, et al. Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support. J Thorac Cardiovasc Surg 1997;114:1053-60.

23. Larsen BM, Goonewardene LA, Joffe AR, et al. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. Clin Nutr 2012;31:322-9.

24. Larsen BM, Field CJ, Leong AY, et al. Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants. JPEN J Parenter Enteral Nutr 2015;39:171-9.

25. Lekmanov AU, Erpuleva UV, Zolkina IV, Rossaus PA. [Study of glutamine solution use efficiency in pediatric patients with heavy thermic burns and concomitant injuries in the intensive care unit]. Anesteziol Reanimatol 2013:49-51.

26. Vanwijngaerden YM, Langouche L, Brunner R, et al. Withholding parenteral nutrition during critical illness increases plasma bilirubin but lowers the incidence of biliary sludge. Hepatology 2014;60:202-10.

27. Vanwijngaerden YM, Wauters J, Langouche L, et al. Critical illness evokes elevated circulating bile acids related to altered hepatic transporter and nuclear receptor expression. Hepatology 2011;54:1741-52.

28. Jenniskens M, Langouche L, Vanwijngaerden YM, Mesotten D, Van den Berghe G. Cholestatic liver (dys)function during sepsis and other critical illnesses. Intensive Care Med 2015; Sep 21. [Epub ahead of print]

29. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature 2011;469:323-35.

30. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. Cell Metab 2009;10:507-15.

31. Hermans G, Casaer MP, Clerckx B, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med 2013;1:621-9.

Supplementary appendix

Early versus Late Parenteral Nutrition in Critically Ill Children

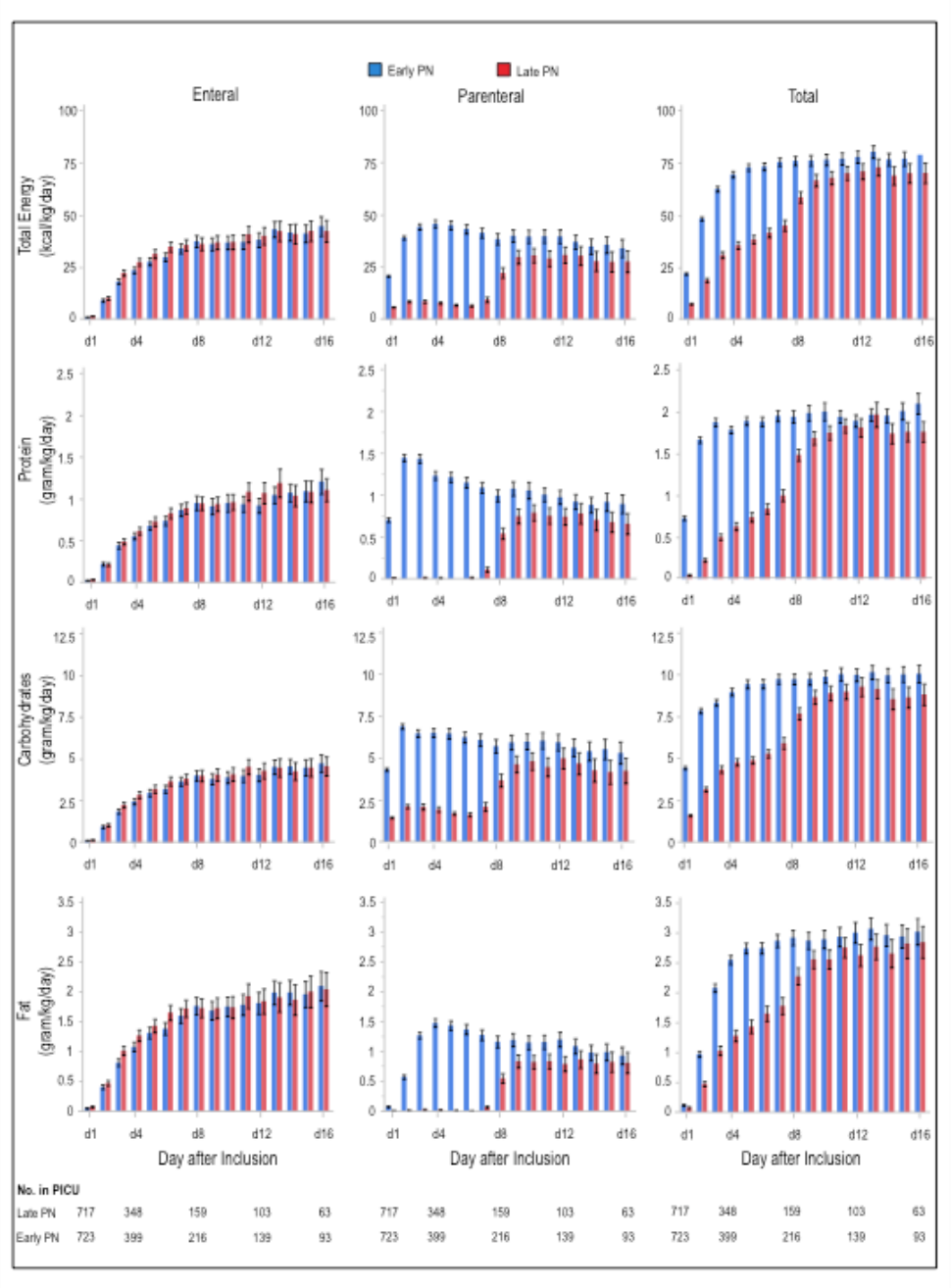
---

Tom Fivez MD[1]*, Dorian Kerklaan MD[2]*, Dieter Mesotten MD, PhD[1]*, Sascha Verbruggen MD, PhD[2]*, Pieter J. Wouters MSc[1], Ilse Vanhorebeek PhD[1], Yves Debaveye MD, PhD[1], Dirk Vlasselaers MD, PhD[1], Lars Desmet MD[1], Michael P. Casaer MD, PhD[1], Gonzalo Garcia Guerra MD, MSc[3], Jan Hanot MD[1,3], Ari R. Joffe MD[3], Dick Tibboel MD, PhD[2], Koen Joosten MD, PhD[2], Greet Van den Berghe MD, PhD[1]

* *contributed equally, alphabetical order*

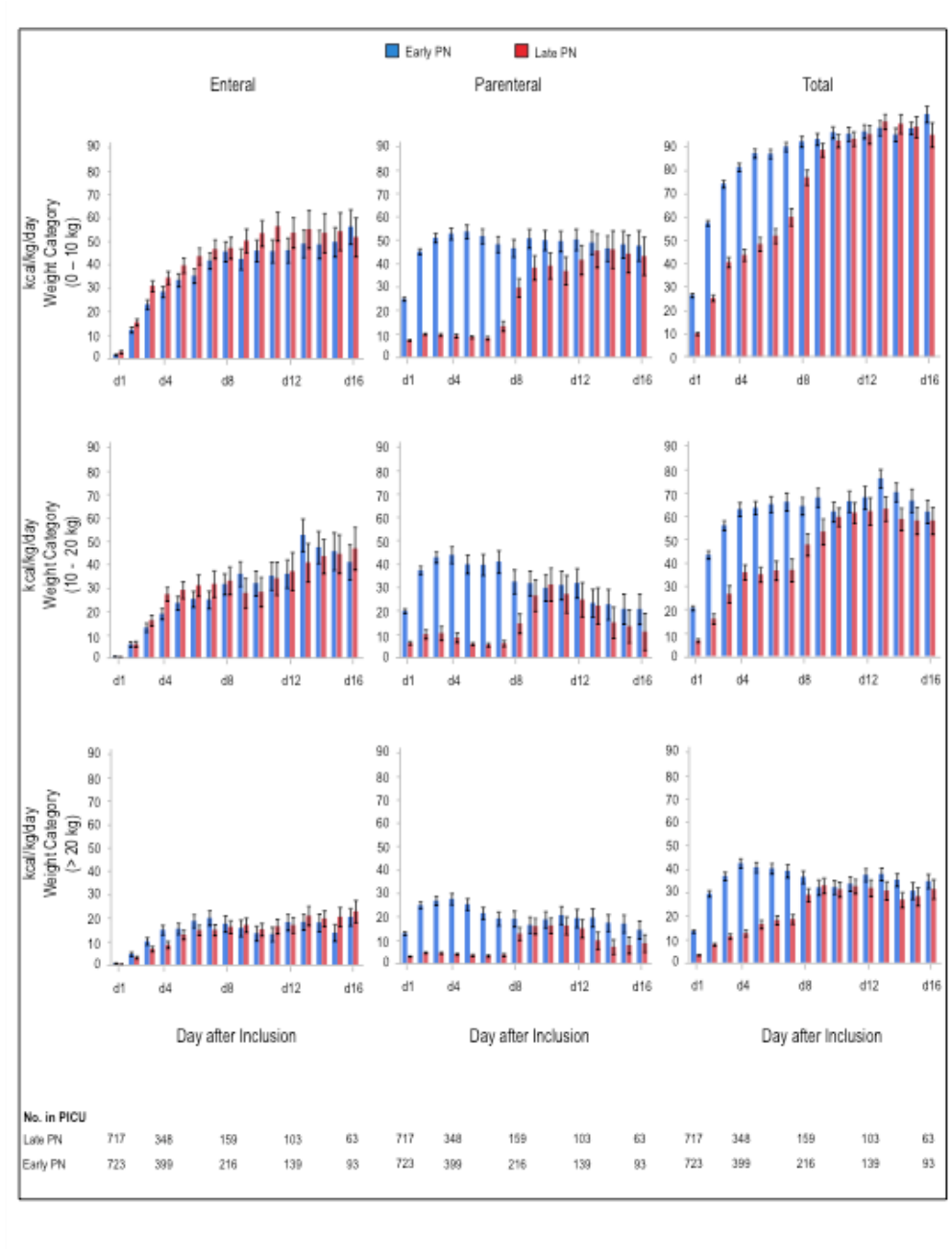
Supplementary Figure 1. *Caloric and macronutrient intake per kg*

Daily amount of energy in kcal/kg/day, and the daily amounts of substrates in g/kg/day, for the first 16 days of pediatric intensive care unit (PICU) stay provided by the enteral route, the parenteral route or both (total). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the late parenteral nutrition (PN) group; the blue bars represent the early PN group.



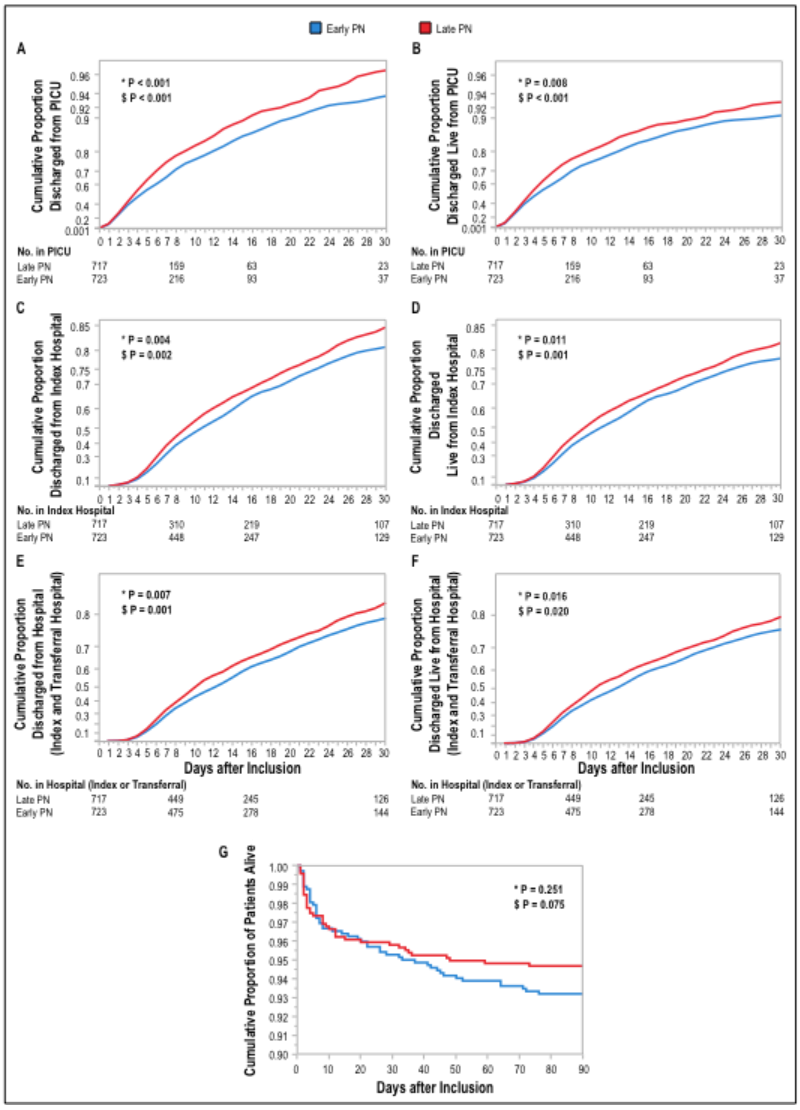
Supplementary Figure 2. *Caloric intake per kg for weight categories*

Daily amount of energy in kcal/kg/day, for three weight categories (<10 kg, 10-20 kg and >20 kg), for the first 16 days of pediatric intensive care unit (PICU) stay provided by the enteral route, the parenteral route or both (total). Bars represent the mean and the whiskers represent the standard error of the mean (SEM). The red bars represent the late parenteral nutrition (PN) group; the blue bars represent the early PN group.



Supplementary Figure 3. *Kaplan-Meier plots for the time to (live) discharge from the PICU and the hospital and for survival up to 90 days*

Panels A to F represent the cumulative proportions of patients discharged from the PICU (A), discharged *live* from the PICU (B), discharged from the hospital [index (C) and total (E)] and discharged *live* from the hospital [index (D) and total (F)]. For the analyses of the time to discharge, data for all patients were censored at 90 days, while non-survivors were censored at time of death. For the analyses of the time to *live* discharge, data were censored at 90 days with non-survivors censored at 91 days to account for death as a competing risk. For sake of clarity, only the first 30 days are shown in panels A-F. Panel G illustrates survival up to 90 days. The red lines represent the late PN group; the blue lines represent the early PN group.



*univariable log-rank P-value; $ P-value adjusted in multivariable analysis.

Supplementary Table 1. *Exclusion criteria for study participation*

Not critically ill enough to necessitate nutritional support
STRONGkids score lower than 2 on PICU admission[1]
Non-pediatric patients (aged 17 or older)
Premature newborns (<37 weeks gestational age upon admission in the PICU)
'Do not resuscitate' code at the time of PICU admission
Expected death within 12 hours
Readmission to PICU after already having been randomized
Enrollment in another intervention trial
Transfer from another PICU or neonatal ICU after a stay of more than 7 days
Ketoacidotic or hyperosmolar coma
Inborn metabolic diseases requiring specific diet
Short bowel syndrome or other conditions requiring PN for more than 7 days prior to PICU admission

PICU=Pediatric Intensive Care Unit, PN=Parenteral Nutrition

Supplementary Table 2. *Local protocols for initiation of PN in early PN group, in all participating centers EN was attempted as soon as possible*

Center	On admission	Day 2	Day 3	Subsequent Stay
Leuven, Belgium	Mixture of glucose 30% and Vaminolact® (Fresenius)	Addition of lipids (SMOFlipid® Fresenius)	All replaced by mixture of glucose 50% and SMOFlipid® with Vaminolact® or Vamin 18®.	Glucose 50% and SMOFlipid® with Vaminolact® or Vamin 18®
Rotterdam, The Netherlands	Continuous glucose infusion with glucose intake 4-6 mg/kg/min (< 30 kg) or 2-4 mg/kg/min (> 30 kg)	Pharmacy-made PN: mixture of glucose, Primene® (Baxter) and Intralipid® (Baxter, 50% of final dose). Children >30 kg Olimel® (Baxter, N5 or N4 depending on central or peripheral line)	Increase of lipids to 100%	Pharmacy-made PN: mixture of glucose, Primene® (Baxter) and Intralipid® (Baxter, 100% of final dose). Children >30 kg Olimel® (Baxter, N5 or N4 depending on central or peripheral line)
Edmonton, Canada	Continuous glucose infusion with glucose intake 3-4 mg/kg/min	Addition of 20% IV lipids (50% of final dose)	Increase of lipids to 100% Mixture amino acids and concentrated glucose	Mixture amino acids, concentrated glucose and 20% IV lipids

EN=enteral nutrition, IV=intravenous, PN=parenteral nutrition

Supplementary Table 3. *Macronutrient and caloric targets per center*

Center	First day	Subsequent stay
Leuven, Belgium	First 10 kg: 100 kcal/kg 10-20 kg: + 50 kcal/kg >20 kg: + 20 kcal/kg (adjusted downward when fluid restriction required)	
Rotterdam, The Netherlands	EN: basal metabolic rate by Schofield-weight[2] PN: ESPGHAN[3]	EN: Recommended Dietary Allowances[4] PN: ESPGHAN[3]
Edmonton, Canada	Resting energy expenditure by indirect calorimetry If indirect calorimetry impossible: 65% of basal metabolic rate (FAO-WHO[5])	Adjusted daily by the dietitian based on clinical information

EN=enteral nutrition, PN=parenteral nutrition

Supplementary Table 4. *Protocol for scoring of infections*

---

1. **Data export**
   All patients receiving antimicrobial agents were identified by the datamanager, who provided an export of all patient numbers with all the information on antimicrobial agents given as well as the duration of such treatment.

2. **Identification of patients with infections**
   The infectious disease specialists, who were blinded for treatment allocation, selected all patients receiving antimicrobial agents for more than 48h, after excluding all patients who received prophylaxis. Each patient who fulfilled the criteria for infection, as well as the type of infection, was identified as such based on thorough review of the medical record[6]. Patients for whom antimicrobials where initiated prior to PICU admission or within the first 48 hours of admission while the criteria for infection were fulfilled, were labeled as "*having an infection upon admission*". When antimicrobial agents were initiated after randomization and beyond the first 48 hours in the PICU, and were given for more than 48 hours while the criteria for infection were fulfilled, the patient was labeled as "*having a new infection*"[6].

Supplementary Table 5. *Logistic regression and Cox proportional hazards analyses*

	OR or HR unadjusted (95% CI) Late PN vs. Early PN	P-value unadjusted	OR or HR adjusted* (95% CI) Late PN vs. Early PN	P-value adjusted
Primary Outcomes				
Odds for New Infection	0.53 (0.39-0.71)	< 0.001	0.48 (0.35-0.66)	< 0.001
Likelihood of Earlier Live Discharge from PICU	1.14 (1.02-1.27)	0.01	1.23 (1.11-1.37)	< 0.001
Safety Outcomes				
Odds for Death				
Within 8 days in PICU	0.91 (0.48-1.71)	0.76	0.73 (0.34-1.51)	0.39
During PICU Stay	0.89 (0.55-1.45)	0.64	0.73 (0.42-1.28)	0.27
During Hospital Stay	0.84 (0.53-1.32)	0.44	0.72 (0.43-1.19)	0.20
Within 90 days after enrollment	0.77 (0.49-1.19)	0.23	0.64 (0.39-1.05)	0.07
Secondary Efficacy Outcomes				
Likelihood of Earlier Live Weaning from Mechanical Ventilatory Support	1.11 (1.00-1.24)	0.04	1.19 (1.07-1.32)	0.001
Odds for Renal Replacement Therapy	0.69 (0.37-1.26)	0.23	0.49 (0.24- 0.96)	0.03
Likelihood of Earlier Live Discharge from Index Hospital	1.14 (1.03-1.27)	0.01	1.19 (1.07-1.33)	0.001
Likelihood of Earlier Live Discharge from Hospital (Index and Transferral Hospital)	1.14 (1.02--1.27)	0.02	1.21 (1.08-1.34)	<0.001

All duration of care outcomes were censored at 90 days with non-survivors censored at 91 days.
OR=Odds Ratio, HR=Hazard Ratio, PN=parenteral nutrition, 95% CI= 95% confidence intervals, PICU=pediatric intensive care unit

* Adjusted for the following risk factors: center, age group, diagnosis group, PELOD score (first 24h)[7] and STRONGkids category[1]

Supplementary Table 6. *P-values for interaction between randomized treatment allocation and the predefined baseline risk factors on the primary outcomes*

	P-value
Patients with New Infections[1]	
PELOD score first 24h in PICU	0.80
Age group	0.55
Diagnostic group	0.25
STRONGkids score[1]	0.11
Center	0.72
Time to live discharge from the PICU[2]	
PELOD score first 24h in PICU	0.80
Age group	0.65
Diagnostic group	0.73
STRONGkids score[1]	0.19
Center	0.56

PELOD=PEdiatric Logistic Organ Dysfunction[7], PICU=Pediatric Intensive Care Unit
[1] Multivariable Logistic Regression Analysis censored at 90 days with non-survivors censored at 91 days
[2] Multivariable Cox Proportional Hazard Analysis censored at 90 days with non-survivors censored at 91 days

Supplementary Table 7. *Adjusted Odds Ratios and Hazard Ratios further corrected for hypoglycemia (plasma concentration glucose < 40 mg/dL) and for the amount of of enteral feeding (kcal/kg/day) during randomisation window*

	OR or HR adjusted* (95% CI) Late PN vs. Early PN (adjusted for hypoglycemia)	**P-value**	**OR or HR adjusted* (95% CI) Late PN vs. Early PN (adjusted for enteral kcal/kg/d)**	**P-value**
Primary Outcomes				
Patients with New Infections	0.45 (0.32-0.62)	< 0.001	0.47 (0.34-0.65)	< 0.001
Likelihood Earlier Live PICU Discharge	1.26 (1.13-1.41)	< 0.001	1.24 (1.12-1.38)	< 0.001
Secondary Efficacy Outcomes				
Likelihood Earlier Live Weaning from Mechanical Ventilatory Support	1.21 (1.09-1.35)	< 0.001	1.19 (1.07-1.32)	0.001
Renal Replacement Therapy	0.49 (0.24- 0.97)	0.03	0.52 (0.25-1.03)	0.06
Likelihood Earlier Live Hospital Discharge	1.22 (1.09-1.36)	< 0.001	1.19 (1.07-1.33)	0.001

All duration of care outcomes were censored at 90 days with non-survivors censored at 91 days. OR=Odds Ratio, HR=Hazard Ratio, PN=Parenteral Nutrition, 95% CI= 95% Confidence Intervals, PICU=Pediatric Intensive Care Unit

* Adjusted for the following risk factors: center, age group, diagnosis group, PELOD score first 24h[7], STRONGkids category[1] and hypoglycemia (plasma concentration glucose < 40 mg/dL) or amount of enterally adminstered kcal per kg per day.

In both analyses, experiencing hypoglycemia and receiving a higher amount of enterally adminstered kcal per kg per day were independent risk factors for infections and for a delayed live discharge from PICU (all P≤0.004).

Supplementary table 8. *Highest plasma concentrations during PICU stay for markers of liver dysfunction and inflammation. Mean plasma glucose concentration during PICU stay*

Highest plasma concentration during PICU stay	**Early PN** N=723	**Late PN** N=717	**P-value**
Liver dysfunction - mean (SEM)			
Highest plasma bilirubin – mg/dL (N = 1258)	1.6 (0.1)	1.9 (0.2)	0.006
Highest plasma Alkaline Phosphatase (N=1231)	194 (5)	181 (6)	<0.001
Highest plasma GGT – IU/L (N = 1221)	85 (7)	62 (5)	0.003
Highest plasma ALT – IU/L (N = 1266)	85 (9)	118 (20)	0.89
Highest plasma AST – IU/L (N = 1264)	202 (28)	271 (48)	0.87
Inflammation- - mean (SEM)			
Highest plasma CRP – mg/L (N = 1303)	86 (4)	93 (4)	0.07
Mean plasma glucose – mg/dL (N= 1391)	117 (1.5)	100 (1.2)	<0.001

PN=Parenteral Nutrition, PICU=Pediatric Intensive Care Unit, SEM= Standard Error of the Mean, GGT= Gamma-Glutamyltransferase, ALT= Alanine Aminotransferase, AST= Aspartate Aminotransferase, CRP= C-reactive protein

References

1. Hulst JM, Zwart H, Hop WC, Joosten KF. Dutch national survey to test the STRONGkids nutritional risk screening tool in hospitalized children. Clin Nutr 2010;29:106-11.
2. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr 1985;39 Suppl 1:5-41.
3. Koletzko B, Goulet O, Hunt J, et al. 1. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). J Pediatr Gastroenterol Nutr 2005;41 Suppl 2:S1-87.
4. Dietary Reference Intake: energy, protein and digestible carbohydrates, . Health Council of the Netherlands: The Hague2001.
5. Energy and protein requirements. Report of a joint FAO/WHO/UNU Expert Consultation. World Health Organ Tech Rep Ser 1985;724:1-206.
6. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. American journal of infection control 2008;36:309-32.
7. Leteurtre S, Duhamel A, Salleron J, et al. PELOD-2: an update of the PEdiatric logistic organ dysfunction score. Crit Care Med 2013;41:1761-73.

8. General Conclusions and Perspectives

The central research question of this PhD project is how physicians should feed critically ill children, who have been admitted to the PICU. It is common sense to try enteral nutrition (EN), if the gastrointestinal tract can tolerate it, from admission onwards. However, EN is often insufficient to meet caloric needs, creating a caloric deficit. The latter builds up over time when EN is failing. To compensate for this caloric deficit, parenteral nutrition (PN) can be initiated. Conversely, one can ask to what extent a caloric deficit should be tolerated, since dosing and timing of PN in critically ill children is controversial.

Through a systematic review(1) and a global survey(2) we gauged, respectively, the evidence for and the current practice of supplementary PN in critically ill children.

In the systematic review we only searched for randomized controlled trials (RCT), comparing different dosing or timing of PN. PN was broadly defined as any type of intravenously administered macronutrient: carbohydrate, lipid or protein. Observational studies were not included in the systematic, as they cannot distinguish association from causality. Nevertheless, literature in nutrition in critically ill children has traditionally focused on the relationship between nutritional intake and outcome.(3) Only 6 smaller RCT's, comparing different dosing of macronutrients, could be identified. Besides the limited quantity of the evidence, RCT's had multiple limitations. First, they all focused on intermediate or surrogate endpoints, instead of hard clinical outcome measures. Surrogate outcome measures, such as nitrogen balances and inflammatory markers, are commonly used in clinical nutritional studies.(4-6) While these surrogate outcome measures may give an indication on the effects of a certain treatment, they can be very misleading as well. This is explained by the fact that the tested treatment may have unnoticed side-effects that are not picked up by the surrogate endpoint. For example, studies on the use of steroids in acute respiratory distress syndrome (ARDS) showed improved lung compliance and better lung injury scores.(7, 8) However, steroids did not improve mortality in large multicenter trials.(9) Hyperglycemia or myopathy, known side-effects of steroid administration, may have offset its beneficial effects. Also, administration of high doses of growth hormone in prolonged critically ill patients increased

the levels of markers of anabolism, but doubled the mortality rate in these patients.(10) Second, all of the RCT's were underpowered to detect differences in (surrogate) outcome measures, due to the low number of included patients. Third, even within the limited number of studies, the treatment comparisons were vastly different, looking at effects of different dosing of either proteins or lipids. Hence, no meaningful conclusion can be drawn from the existing literature to support any current practice of supplemental PN in critically ill children. This was in line with an older systematic review on the effects of nutritional strategies (EN and PN) on hard clinical outcome measures.(11)

The lack of strong evidence may have contributed to the highly varying and inevitably weaker guidelines concerning PN for critically ill neonates to critically ill adolescents. We hypothesized that these equivocal guidelines result in a highly variable practice of nutritional support.(2) This was assessed in an international survey, distributed online through the network of The World Federation of Pediatric Intensive and Critical Care Societies and translated in Spanish, Chinese and French to maximize response rate. A point-prevalence survey on nutritional data collected in all patients present in a PICU on a single day was done to verify whether real life practice differed from local protocols. The most stunning finding from the survey was that only in half of the responding PICUs a nutritional protocol was in use. Calculations of energy requirements, needed to set caloric goals, are also based on different equations. Indirect calorimetry, the gold standard to set caloric goals according to the guidelines, was only used in 14% of the PICUs, which was comparable to a previous survey.(12) One can already deduct that, if the setting of the caloric goal differs enormously, the interpretation of caloric deficit and its treatment, is more difficult. All PICUs advocated early initiation of EN, while starting PN within 48 hours after admission was preferred in only 55% of PICUs. The point-prevalence survey nicely demonstrated that success of EN in critically ill children is overestimated. Lack of medical evidence may have given more weight to other drivers for nutritional support. For example, countries with a lower socio economic status already prefer late initiation of PN due to limited availability and higher cost of PN. Hence, we had

to conclude that even the limited available guidelines are not consistently followed and that high-quality evidence is urgently needed to guide clinical practice.

Such a shift from almost dogmatic guidelines, based on low-quality evidence (observational studies, small RCTs with surrogate endpoints), to a practice based on high-quality RCTs, sufficiently powered to detect differences in clinical outcome measures, has taken place over the last 5 years in the adult ICU world. The EPaNIC trial (n=4640) was the first to study the timing to initiate PN in critical ill adults.(13) The other large RCTs, with slightly differing study protocols, such as the SPN(14) and the early PN trial(15) followed soon. While the ideal timing of supplemental PN remains uncertain in critically ill adults, there is now consensus that PN can be safely withheld during the first week of critical illness.(16) Our survey showed that only 3.5% of PICUs would wait at least 7 days to start supplemental PN.

Mechanistic research from the EPaNIC trial revealed that suppression of autophagy by the early administration of PN may be the main driver for the harmful effects of PN.(17) Moreover, tolerating a caloric deficit early during critical illness did not worsen muscle wasting, but reduced ICU acquired muscle weakness. Muscle wasting is the primary rationale for supplemental PN when enteral nutrition fails. It is presumed that caloric deficits force patients to rely on their own protein reserve. Children are especially vulnerable as their energy stores are limited. Therefore, we wanted to investigate the role of ultrasonography to quantify muscle mass wasting in children.(18) Muscle wasting is a typical feature of ICU acquired weakness, which is a combination of critical illness polyneuropathy and critical illness myopathy.(19, 20) Its presentation is typically symmetrical and affects mostly the proximal limbs and the respiratory muscles. In adults the Medical Research Council (MRC) sum score is used to quantify muscle weakness with good reproducibility. However, this volitional measurement is only possible in non-sedated and cooperative patients. In children aged less than 6 years not a single strength measurement has been validated.(21) Electrophysiological testing, including electromyography and

nerve conduction studies, have been proposed.(22) This is however time consuming, not readily available in most hospitals, not standardized in children and often not feasible. An alternative technical diagnostic for muscle wasting in ICU is ultrasonography of skeletal muscle, has been validated in adult ICU patients.(23, 24) Therefore we investigated whether ultrasonography might be useful to detect muscle mass reduction in children and this in comparison with adults. Muscle thickness of the m quadriceps in critically ill adults and children was tested by two independent investigators. Ultrasonographical measurement of muscle thickness in critically ill children can easily be done in sedated critically ill children and adults with low inter-observer variability. However, the moderate accuracy and high intra-observer variability do not allow reliably detecting a decrease of less than 30% in muscle thickness in the pediatric ICU population. In adults we found acceptable inter- and intra-observer variability, in line with other publications.(25, 26) Further research is necessary to optimize ultrasonography protocols to diagnose muscle wasting in critically ill children. It is nonetheless important not to focus only on the muscle mass reduction as we know from the adult population the quality of the muscle tissue is more important for muscle strength than the quantity.(27) Hence ultrasonographical assessment of muscle quality may be a better marker for muscle weakness.(28) In our study population the images obtained from those patients who were the sickest and admitted for a longer period were totally different. In these patients it was far more difficult to distinguish the individual components, adipose tissue, muscle and subcutis. Further developments in ultrasonography could help the clinician to identify the patients at risk and whether a certain type of nutritional support is beneficial in terms of muscle quality.

In the third part of my PhD project we examined whether a strategy of withholding PN during the first week of critical illness is superior to strategy of early initiation of PN when enteral nutrition is insufficient to compensate the caloric deficit. During a period of 3 years we included 1440 patients (term newborns to 17 years old) in the PEPaNIC trial. The PEPaNIC trial was sufficiently powered to detect differences

in clinical outcome measures (incidence of new infections in PICU and the length of stay in PICU). Also its statistical analysis plan was published in advance.

All patients admitted to the PICU in the three participating centres (Dept Intensive Care Medicine Leuven, Sophia Children's Hospital Rotterdam and Stollery Children's Hospital Edmonton in Canada) were assessed for eligibility on a daily basis. The high PELOD and PRISM scores indicate that those patients who really needed a nutritional plan were included in the trial. The intervention of late PN was exactly similar in the three centers; this was compared with the current standard nutritional support of early PN. The current early PN strategy obviously differed among the 3 centers. The latter underscores the external validity of the trial. The initiation and augmentation of enteral nutrition was similar in both groups. The two randomization groups were nicely balanced, but moreover they represented the wide range of critically ill children concerning admission diagnosis and age. The benefits of late PN were unexpectedly overwhelming. The two primary outcome measures, namely the incidence in new infection and duration of stay, which are a reflection of enhanced recovery, were both markedly reduced. The benefits of late PN were present across all predefined risk factors (PELOD-score, center, age, nutritional risk score and admission diagnosis). This underpins the robustness of the findings and the broad applicability of the late PN strategy. To ascertain the correctness of the study findings, both unadjusted and risk factor adjusted comparisons were done, taking death as a competing risk for earlier discharge or absence of new infection. This was to exclude that new infections were avoided or length of stay was shortened because the patient died. The change of earlier discharge from the PICU and from the index hospital was significantly different and this effect even remained in the transferral hospital. Such a stringent methodology for clinical trials in nutritional research in critically ill children has not been used before. The positive effects of late PN are more pronounced compared to the adult EPaNIC trial.(13) This may be due to the fact that the PICU population is in a way a "cleaner" population. Critically ill children mostly do not suffer from long existing chronic medical diseases.

Interestingly inflammation, reflected in higher CRP levels, was more pronounced in the late PN group, while they had fewer infections. So in essence the inflammatory response is better preserved in a hypocaloric condition, leading to fewer infections. This could underlie the concept that late PN preserves autophagy, which is an essential part of the innate immunity.(29-31) Neonates live on autophagy, because they need the process to go from constant feeding intra-uterine to intermittent feeding once they are born.(32) Newborn animals in which autophagy is eliminated die.(33) This is in line with the finding that the neonates in the PEPaNIC trial benefited the most from a late PN strategy.

As usual, new findings from clinical studies raise new questions and future perspectives.

From the PEPaNIC trial it is clear that closing the caloric deficit early by the administration of PN, is harmful. Post-hoc analyses of the EPaNIC trial in critically ill patients revealed that there is dose-dependency of the harmful effects of PN.(34) In patients with contraindications for EN, late PN had the strongest treatment effect.(13) The lower doses of macronutrients were associated with faster recovery. Whether this dose-dependency is also present in critically ill children is unclear.

The EPaNIC post-hoc analyses also hinted that the amount of amino acids/proteins may be responsible for the delayed recovery in critically ill adults. This may be contra-intuitive as proteins are regarded as essential to maintain muscle mass. However, proteins are also strong suppressors of autophagy, which may reduce the quality of skeletal muscle. Isotope studies in critically ill adolescents showed that high protein intake increased gluconeogenesis and lipolysis.(35) Increased glucose production and lipolysis my worsen insulin resistance and hyperglycemia, which are also linked with poor outcome. The PEPaNIC RCT was not set up to evaluate the role of the individual macronutrients. However, as the control group of early PN differed among the three centers, post-hoc analyses may give an indication whether carbohydrates, lipids or proteins are the main culprits for delayed recovery with early PN.

In our trial we only focussed on PN, the question raises if early EN is also harmful. This is even more controversial. Obviously when a child can be fed enterally, physicians will always do so and should do;

as this will be in line with the severity of illness. The sicker a child is the more difficult it is to feed it. But what to do with prokinetics? Should we start them at all? The children with the highest nutritional risk benefitted the most from late PN. Moreover in the adult EPaNIC trial late PN was even more beneficial in the group of patients who could not be fed enterally.(13) Additionally, large RCTs such as the EDEN and the CALORIES trial demonstrated that an aggressive EN strategy is certainly not beneficial for the critically ill adult.(36, 37) In my opinion this all points in one direction, namely that we do not need to force enteral nutrition in our patients.

Conducting a large, international, multicenter trial with hard clinical outcomes like the PEPaNIC is a true challenge. Highly standardized protocols with a clear difference between the control group and the intervention group are the necessary foundations of the trial. The whole medical, nursing and dieticians' team has to be willing to make a success of the trial, through strict protocol compliance and direct communication with the trial coordinators. One can only be willing to make it a success of something if he or she understands the essence of the research question and hence the need of the trial. Frequent presentations to bedside doctors and nurses to familiarize them with the protocol are indispensable. In order to prevent selection bias the trial coordinators need to screen the entire population to assure that every patient who fits the inclusion criteria, is approached for consent. Asking the consent is time consuming but crucial, as parents have many questions about the trial but also about their child's stay in intensive care. So in each participating center there has to be a local trial coordinator who is at all time in contact with the central trial coordinator. In essence the success of the multicentre aspect depends on the strength of the alliance between the different partners and this on all levels.

In contrast with our PEPaNIC trial, in the past 4 years there have been many multicenter trials in the adult ICU published that are neutral. A neutral trial can be very valuable, provided that the trial is well conducted. Poor protocol compliance, non-realistic power calculations and poor inclusion rate per center are the main reasons of failure for many trials. For the community and medicine in se it is however

crucial that well designed multicenter trials with enough statistical power and appropriate outcome measures provide the necessary medical evidence to improve standard of care worldwide.

Summary

Nutrition for children is needed for maintaining all the processes in the body and for growth.
Nutrition can be subdivided in macronutrients and micronutrients. Macronutrients comprise proteins, lipids and carbohydrates. Micronutrients encompass trace elements and vitamins.

When a child is admitted to the PICU it is often not capable to eat. Therefore physicians initiate artificial nutrition. This can be done through a gastric tube which is the most natural way of providing nutrition. However caloric targets are often not reached due to gastrointestinal intolerance. To meet the caloric needs, parenteral nutrition, which is given intravenously, is often started.

When and how much parenteral nutrition should be given, is the question of this PhD. We did a systematic review to gather all scientific evidence, supporting the dosing and timing of PN. We only found 6 smaller randomized controlled trials, looking at surrogate endpoints such as nitrogen balances and inflammation to evaluate the effects of different PN regimens. All studies were statistically underpowered due to their small size. Hence, there was no scientific evidence at all to guide the initiation, dosing of supplemental PN. We hypothesized that the lack of sound evidence should result in a very variable daily practice worldwide. We therefore performed an international survey. Results were striking. In half of the pediatric intensive care units there was no nutritional protocol. Dosing and timing were also very variable. Moreover, as PN is expensive, countries with a lower socio economic status reported more frequently late initiation of PN.

To evaluate whether PN should be started within the first week of critical illness, we conducted a large international randomized controlled trial. During 3 years 1440 children were included in the PEPaNIC trial, at 3 study sites: Leuven, Rotterdam, NL and Edmonton, Canada. The current practice of supplying

PN, which was slightly different in each center, was compared with the same intervention, namely no PN during the first week of critical illness and only providing maintenance fluid.

The incidence of new infection and duration of stay were markedly reduced when PN was omitted during the first week of pediatric critical illness. The results where independent of predefined risk factors, such as severity of illness, reason for admission, age and study center. When you initiate PN during the first week of critical illness, you impair the child's chances of recovery. One might have concerns that not giving PN to the most vulnerable children, namely neonates and the children with a high nutritional risk, would harm them. Surprisingly the beneficial effects of not giving PN to these children were even more pronounced.

How can this be explained? One of the responsible mechanism is autophagy. It is an essential part of the innate immune system and also responsible for quality control in cells. Suppression of autophagy, leading to defective clearance of damaged cell organelles, could be the driver behind the clinical effects of the trial.

Not substituting the caloric deficit could force patients to rely on their own reserves. Clinically this would result in slower recovery and loss of muscle mass tissue, as this a major source of proteins. With our trial we proved that recovery is enhanced instead of hampered. To analyze muscle mass in critically ill adults, ultrasonography is an accessible and easy tool. However, in critically ill children this technique has not been validated. Therefore, we investigated whether ultrasonography is reliable to use in critically ill children. Our results showed that the intra-observer variability - the difference between two measurements done by the same investigator - was too high when taking into account the expected loss of muscle mass. In my opinion, future research on the diagnosis of muscle weakness should also look at the quality of the muscle instead of the quantity. As we know from adult studies that apart from the

loss itself it is especially the changes in muscle tissue quality that are responsible for the resulting muscle weakness.

In conclusion we advise to tolerate a caloric deficit during the first week of critical illness in PICU, when enteral nutrition is insufficient.

Samenvatting

Kinderen hebben voeding nodig om in leven te blijven en te groeien. Voeding wordt onderverdeeld in macronutriënten en micronutriënten. De macronutriënten bestaan uit eiwitten, suikers en vetten. Vitaminen en sporenelementen vormen op hun beurt de micronutriënten.

Wanneer een kritiek ziek kind opgenomen wordt op intensieve zorgen is het vaak niet in staat om te eten. Daarom zullen kinderintensivisten kunstmatige voeding starten. Vooreerst door sondevoeding, bij het jonge kind flesvoeding of borstvoeding toe te dienen via de maagsonde hetgeen we enterale voeding noemen. Tijdens kritieke ziekte wordt deze enterale voeding echter vaak minder goed verdragen, hetgeen ervoor zorgt dat een calorisch deficit ontstaat. Om dit deficit te vermijden, wordt er vaak parenterale voeding gestart dewelke gegeven wordt via een intravenueze lijn in een grote lichaamsader.

Wanneer deze parenterale voeding dient gestart te worden en hoeveel er gegeven moet worden, vormt het onderwerp van dit doctoraat. Om inzicht te krijgen in de huidige wetenschappelijke evidentie omtrent dit onderwerp, hebben we op een systematische wijze de alle systematische en gerandomiseerde trials (RCT) verzameld in een systematic review. We konden slechts 6 RCT's weerhouden die allen methodologisch zwak waren. Op basis van deze RCT's kunnen dan ook op geen enkele wijze gevalideerde richtlijnen aangaande dit onderwerp geformuleerd worden. Om na te gaan of dit gebrek aan duidelijke richtlijnen aanleiding geeft tot een zeer variabele praktijk wereldwijd, deden we een enquête omtrent voeding op kinderintensieve. We kregen antwoord vanuit 52 landen en dit van 156 kinderintensieve afdelingen. De resultaten gaven aan dat de variabiliteit aangaande voedingsbeleid op kinderintesieve bijzonder groot is en dat zelfs de helft van de centra toegaf dat ze geen voedingsprotocol voorhanden hadden.

Om dus een gefundeerd antwoord te kunnen verschaffen op de vraag of parenterale voeding moet gestart worden gedurende de eerste week van kritieke ziekte bij kinderen, voerden we een grote internationale studie uit in Leuven, Rotterdam en Edmonton. In totaal werden over een periode van 3 jaar 1440 kinderen geïncludeerd. Het huidige voedingsbeleid van de drie centra, die uiteraard onderling verschilden, werden vergelijken met één en dezelfde interventie groep. Deze interventie bestond erin om geen parenterale voeding tijdens de eerste week van kritieke ziekte te geven en enkel onderhoudsvocht toe te dienen. De resultaten van deze RCT zijn opzienbarend. De incidentie van nieuwe infecties evenals de verblijfsduur op kinderintensieve en in het ziekenhuis werden aanzienlijk verminderd. Dit effect was onafhankelijk van verscheidene risicofactoren waaronder bv het centrum, hetgeen aangeeft dat het schadelijk is om parenterale voeding toe te dienen tijdens de eerste week van kritieke ziekte. Bij kinderen met een hoog risico op ondervoeding en de neonaten was dit schadelijk effect zelfs nog meer uitgesproken. Hoe kan men dit verklaren? Een van de mogelijke mechanismen is autofagie. Dit is een essentieel onderdeel van de aangeboren immuniteit en vitaal voor de controle van de cel kwaliteit. Onderdrukken van autofagie kan deels de klinische effecten vastgesteld in onze studie verklaren.

Het toelaten van een calorisch deficit kan patiënten forceren om terug te vallen op hun eigen endogene reserves. Klinisch zou dit resulteren in een vertraagd herstel een verlies aan spiermassa. We toonden echter aan dat het herstel werd bespoedigd door geen PN te starten. Bij volwassenen is reeds aangetoond dat echografie betrouwbaar is om spiermassa verlies te diagnosticeren. Bij kinderen werd dit bij ons weten nog nooit nagegaan. Daarom hebben we dit op systematische wijze onderzocht bij volwassenen en kinderen. De resultaten wijzen uit dat de intra-observer variabiliteit te groot is om het verwachte spiermassa verlies te kunnen diagnosticeren. Met ander woorden het verschil tussen twee opeenvolgende metingen uitgevoerd door de dezelfde onderzoeker zijn te groot in vergelijking met de verwachte spiermassareductie om de techniek toe te passen bij kinderen.

Bijkomend onderzoek is dus nog nodig om de massa evenals kwaliteit van het spierweefsel op eenvoudige wijze te kunnen analyseren. Gezien onderzoek bij volwassenen heeft aangetoond het niet zozeer het verlies van spiermassa maar wel de kwaliteit van het resterende spierweefsel bepalend is naar de resterende spiersterkte.

Als conclusie van dit doctoraat adviseren we om geen parenterale voeding te starten bij kinderen op intensieve zorgen gedurende de eerste week van kritieke ziekte.

Bibliography

1. Fivez T, Kerklaan D, Mesotten D, Verbruggen S, Joosten K, Van den Berghe G. Evidence for the Use of Parenteral Nutrition in the Pediatric Intensive Care Unit. Clin Nutr.In press.

2. Kerklaan D, Fivez T, Mehta NM, Mesotten D, van Rosmalen J, Hulst JM, et al. Worldwide Survey of Nutritional Practices in PICUs. Pediatr Crit Care Med. 2015 Oct 26.

3. Alberda C, Gramlich L, Jones N, Jeejeebhoy K, Day AG, Dhaliwal R, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med. 2009 Oct;35(10):1728-37.

4. Larsen BM, Field CJ, Leong AY, Goonewardene LA, Van Aerde JE, Joffe AR, et al. Pretreatment with an intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene b4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants. JPEN J Parenter Enteral Nutr. 2015 Feb;39(2):171-9.

5. Larsen BM, Goonewardene LA, Joffe AR, Van Aerde JE, Field CJ, Olstad DL, et al. Pre-treatment with an intravenous lipid emulsion containing fish oil (eicosapentaenoic and docosahexaenoic acid) decreases inflammatory markers after open-heart surgery in infants: a randomized, controlled trial. Clin Nutr. 2012 Jun;31(3):322-9.

6. Chaloupecky V, Hucin B, Tlaskal T, Kostelka M, Kucera V, Janousek J, et al. Nitrogen balance, 3-methylhistidine excretion, and plasma amino acid profile in infants after cardiac operations for congenital heart defects: the effect of early nutritional support. J Thorac Cardiovasc Surg. 1997 Dec;114(6):1053-60.

7. Meduri GU, Belenchia JM, Estes RJ, Wunderink RG, el Torky M, Leeper KV, Jr. Fibroproliferative phase of ARDS. Clinical findings and effects of corticosteroids. Chest. 1991 Oct;100(4):943-52.

8. Meduri GU, Marik PE, Chrousos GP, Pastores SM, Arlt W, Beishuizen A, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. Intensive Care Med. 2008 Jan;34(1):61-9.

9. Steinberg KP, Hudson LD, Goodman RB, Hough CL, Lanken PN, Hyzy R, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. N Engl J Med. 2006 Apr 20;354(16):1671-84.

10. Takala J, Ruokonen E, Webster NR, Nielsen MS, Zandstra DF, Vundelinckx G, et al. Increased mortality associated with growth hormone treatment in critically ill adults. N Engl J Med. 1999 Sep 9;341(11):785-92.

11. Joffe A, Anton N, Lequier L, Vandermeer B, Tjosvold L, Larsen B, et al. Nutritional support for critically ill children. Cochrane database of systematic reviews. 2009 (2):CD005144.

12. van der Kuip M, Oosterveld MJ, van Bokhorst-de van der Schueren MA, de Meer K, Lafeber HN, Gemke RJ. Nutritional support in 111 pediatric intensive care units: a European survey. Intensive Care Med. 2004 Sep;30(9):1807-13.

13. Casaer MP, Mesotten D, Hermans G, Wouters PJ, Schetz M, Meyfroidt G, et al. Early versus late parenteral nutrition in critically ill adults. N Engl J Med. 2011 Aug 11;365(6):506-17.

14. Heidegger CP, Berger MM, Graf S, Zingg W, Darmon P, Costanza MC, et al. Optimisation of energy provision with supplemental parenteral nutrition in critically ill patients: a randomised controlled clinical trial. Lancet. 2013 Feb 2;381(9864):385-93.

15. Doig GS, Simpson F, Sweetman EA, Finfer SR, Cooper DJ, Heighes PT, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. JAMA. 2013 May 22;309(20):2130-8.

16. Vincent JL, Preiser JC. When should we add parenteral to enteral nutrition? Lancet. 2013 Feb 2;381(9864):354-5.

17. Hermans G, Casaer MP, Clerckx B, Guiza F, Vanhullebusch T, Derde S, et al. Effect of tolerating macronutrient deficit on the development of intensive-care unit acquired weakness: a subanalysis of the EPaNIC trial. Lancet Respir Med. 2013 Oct;1(8):621-9.

18. Fivez T, Hendrickx A, Van Herpe T, Vlasselaers D, Desmet L, Van den Berghe G, et al. An Analysis of Reliability and Accuracy of Muscle Thickness Ultrasonography in Critically Ill Children and Adults. JPEN J Parenter Enteral Nutr. 2015 Mar 9.

19. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. N Engl J Med. 2014 Apr 24;370(17):1626-35.

20. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Clinical review: Critical illness polyneuropathy and myopathy. Crit Care. 2008;12(6):238.

21. Williams S, Horrocks IA, Ouvrier RA, Gillis J, Ryan MM. Critical illness polyneuropathy and myopathy in pediatric intensive care: A review. Pediatr Crit Care Med. 2007 Jan;8(1):18-22.

22. Zifko UA, Zipko HT, Bolton CF. Clinical and electrophysiological findings in critical illness polyneuropathy. Journal of the neurological sciences. 1998 Aug 14;159(2):186-93.

23. Segers J, Hermans G, Charususin N, Fivez T, Vanhorebeek I, Van den Berghe G, et al. Assessment of quadriceps muscle mass with ultrasound in critically ill patients: intra- and inter-observer agreement and sensitivity. Intensive Care Med. 2015 Mar;41(3):562-3.

24. Gruther W, Benesch T, Zorn C, Paternostro-Sluga T, Quittan M, Fialka-Moser V, et al. Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. Journal of rehabilitation medicine. 2008 Mar;40(3):185-9.

25. Puthucheary ZA, Rawal J, McPhail M, Connolly B, Ratnayake G, Chan P, et al. Acute skeletal muscle wasting in critical illness. JAMA. 2013 Oct 16;310(15):1591-600.

26. Campbell IT, Watt T, Withers D, England R, Sukumar S, Keegan MA, et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. Am J Clin Nutr. 1995 Sep;62(3):533-9.

27. Casaer MP, Langouche L, Coudyzer W, Vanbeckevoort D, De Dobbelaer B, Guiza FG, et al. Impact of early parenteral nutrition on muscle and adipose tissue compartments during critical illness. Crit Care Med. 2013 Oct;41(10):2298-309.

28. Heckmatt JZ, Pier N, Dubowitz V. Measurement of quadriceps muscle thickness and subcutaneous tissue thickness in normal children by real-time ultrasound imaging. Journal of clinical ultrasound : JCU. 1988 Mar-Apr;16(3):171-6.

29. Derde S, Vanhorebeek I, Guiza F, Derese I, Gunst J, Fahrenkrog B, et al. Early parenteral nutrition evokes a phenotype of autophagy deficiency in liver and skeletal muscle of critically ill rabbits. Endocrinology. 2012 May;153(5):2267-76.

30. Vanhorebeek I, Gunst J, Derde S, Derese I, Boussemaere M, Guiza F, et al. Insufficient activation of autophagy allows cellular damage to accumulate in critically ill patients. J Clin Endocrinol Metab. 2011 Apr;96(4):E633-45.

31. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature. 2011 Jan 20;469(7330):323-35.

32. Schiaffino S, Mammucari C, Sandri M. The role of autophagy in neonatal tissues: just a response to amino acid starvation? Autophagy. 2008 Jul;4(5):727-30.

33. Komatsu M, Waguri S, Ueno T, Iwata J, Murata S, Tanida I, et al. Impairment of starvation-induced and constitutive autophagy in Atg7-deficient mice. The Journal of cell biology. 2005 May 9;169(3):425-34.

34. Casaer MP, Wilmer A, Hermans G, Wouters PJ, Mesotten D, Van den Berghe G. Role of disease and macronutrient dose in the randomized controlled EPaNIC trial: a post hoc analysis. Am J Respir Crit Care Med. 2013 Feb 1;187(3):247-55.

35. Verbruggen SC, Coss-Bu J, Wu M, Schierbeek H, Joosten KF, Dhar A, et al. Current recommended parenteral protein intakes do not support protein synthesis in critically ill septic, insulin-resistant adolescents with tight glucose control. Crit Care Med. 2011 Nov;39(11):2518-25.

36. Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA. 2012 Feb 22;307(8):795-803.

37. Harvey SE, Parrott F, Harrison DA, Bear DE, Segaran E, Beale R, et al. Trial of the route of early nutritional support in critically ill adults. N Engl J Med. 2014 Oct 30;371(18):1673-84.

Curriculum Vitae

1) Persoonlijke gegevens

Geboren op 5 maart 1982

Gehuwd met Eline Goddeeris

Vader van Marie (°03/04/2011) en Anna (°08/08/2013)

tomfivez@gmail.com

Paternosterstraat 61

3110 Rotselaar

0484 949 700

2) Opleiding Geneeskunde

- Middelbaar onderwijs: Broederschool Sint-Niklaas, richting Latijn-wiskunde gedurende 4 jaar; gevolgd door wetenschappen-wiskunde
- Universitaire opleiding aan de faculteit Geneeskunde aan de K.U.Leuven:
  graad van Arts cum laude (Master) behaald in juni 2007
- Ziekenhuisstages (3de jaar arts): inwendige ziekten te Duffel (AZ Sint-Maarten), heelkunde te Bonheiden (Imelda ziekenhuis), pediatrie te Antwerpen (Jan Palfijn) en gynaecologie te Brugge (AZ Sint-Lucas)
- Na stages voorgedragen als kandidaat voor de prijs van Professor De Groote

3) Specialisatie Anesthesie en Reanimatie

2007-2011: UZ Gasthuisberg, Herestraat 49, 3000 Leuven

coördinator: Prof. Vandermeersch E.

2008-2009: Virga Jesse Ziekenhuis, Stadsomvaart 11, 3500 Hasselt

coördinator: Dr. Jamaer L.

=> Erkenning November 2012

4) Opleiding intensieve Intensieve Zorgen

2011-2015: Departement Intensieve Geneeskunde-UZ Leuven

Paediatric **E**arly versus Late **Pa**renteral **N**utrition **i**n **C**riticall Illness
Multicentre randomised controlled study (**PEPaNIC**)

Promotor: Prof Dieter Mesotten
Copromotor: Prof Greet Van den Berghe

2011-2013: Resident intensieve zorgen
2013-2015: Supervisor intensieve zorgen

⇨ Erkenning November 2013

5) Bijkomende opleiding

2014: Refresher course intensive care

2014: Echocardiography for hemodynamic monitoring

2014: Presentation Skills for medical researchers KULeuven

2013: Biostatistiek cursus KULeuven

2012: Health Technology Assessment training

2011: Good Clinical Practice training course for experienced Researchers

2012: TTE opleiding op de dienst cardiologie gedurende 6 weken

2003: Attesten medisch Engels (CLT)

6) Presentaties:

2014: EAPS congres Barcelona: Muscle thickness ultrasonography in critically ill children: analysis of accuracy

2013: ESICM Parijs: Postponing the administration of parenteral nutrition reduces the need for antifungal therapy: a post-hoc analysis of the epanic

2013: Presentatie PEPaNIC voor de staf intensieve zorgen Edmonton

2012-2015: 3 maandelijkse opleidingssessies voor assistenten en residenten

2012: Presentatie PEPaNIC voor de staf Intensieve Rotterdam

2012: Opleiding verpleegkundigen: voeding van het kritiek ziek kind

2011: Presentatie PEPaNIC voor de staf Intensieve UZLeuven

2010: Sepsis op de PICU (krans op ITE Leuven)

2009: Anesthesie tijdens de zwangerschap (anesthesiekrans Hasselt)

7) Publicaties

Impact van glykemiecontrole en parenterale voeding tijdens kritieke ziekte. **Fivez T**., Casaer M.P., Van den Berghe G. Tijdschr. voor Geneeskunde, 69 nr. 3,2013

Worldwide survey of nutritional practices in pediatric intensive care units. **Fivez T**,Dorian K, Hulst J M, Mesotten D, van Rosmalen J, Mehta N, Van den Berghe G, Joosten K F. M., Verbruggen *S. Pediatr Crit Care Med. 2016 Jan;17(1):10-8*

Evidence for the Use of Parenteral Nutrition in the Pediatric Intensive Care Unit. **Fivez T**, Kerklaan D., Mesotten D, Verbruggen S, Joosten K, Van den Berghe G. in press in Clinical Nutrition

An Analysis of Reliability and Accuracy of Muscle Thickness Ultrasonography in Critically Ill Children and Adults. **Fivez T**, Hendrickx A, Van Herpe T, Vlasselaers D, Desmet L, Van den Berghe G, Mesotten D. JPEN J Parenter Enteral Nutr. 2015 Mar 9

Assessment of quadriceps muscle mass with ultrasound in critically ill patients: intra- and inter-observer agreement and sensitivity.Segers J[1], Hermans G, Charususin N, **Fivez T**, Vanhorebeek I, Van den Berghe G, Gosselink R Intensive Care Med. 2015 Mar;41(3):562-3

Late intravascular migration of a previously well functioning labour epidural catheter. **Fivez T**, Deblonde S, Van de Velde M.Eur J Anaesthesiol. 2010 Jul;27(7):634-6.

Impact of withholding early parenteral nutrition completing enteral nutrition in pediatric critically ill patients (PEPaNIC trial): study protocol for a randomized controlled trial.**Fivez T**, Kerklaan D, Verbruggen S, Vanhorebeek I, Verstraete S, Tibboel D, Guerra GG, Wouters PJ, Joffe A, Joosten K, Mesotten D, Van den Berghe G.Trials. 2015 May 1;16:202

Early versus Late Parenteral Nutrition in Critically Ill Children **Fivez T**, Kerklaan D,Mesotten D, Verbruggen S, Wouters PJ, Vanhorebeek I, Debaveye Y,Vlasselaers D, Desmet L, Guerra GG, Hanot J , Joffe A, Tibboel D, Joosten K, Van den Berghe G in press in NEJM